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**WO 2005/011646 A2**

(54) Title: **ANGIOTENSIN II RECEPTOR BLOCKER DERIVATIVES**

(57) Abstract: Angiotensin II receptor blocker nitroderivatives of formula (I): R-(Y-ONO<sub>2</sub>), (I) having wider pharmacological activity and enhanced tolerability. They can be employed for treating cardiovascular, renal and chronic liver diseases and inflammatory processes.

## TITLE OF THE INVENTION

**"ANGIOTENSIN II RECEPTOR BLOCKER DERIVATIVES"**

\*\*\*\*\*

The present invention relates to Angiotensin II  
5 Receptor Blocker (ARB) derivatives. More particularly, the  
present invention relates to ARB nitroderivatives,  
pharmaceutical compositions containing them and their use  
for the treatment of cardiovascular, renal and chronic  
liver diseases, inflammatory processes and metabolic  
10 syndromes.

With the angiotensin II receptor blockers a class of  
compounds is intended, comprising as main components  
Losartan, EXP3174, Candesartan, Telmisartan, Valsartan,  
Eprosartan, Irbesartan and Olmesartan.

15 ARBs are approved only for the treatment of  
hypertension, the antihypertensive activity is due mainly  
to selective blockade of AT<sub>1</sub> receptors and the consequent  
reduced pressor effect of angiotensin II. Angiotensin II  
stimulates the synthesis and secretion of aldosterone and  
20 raises blood pressure via a potent direct vasoconstrictor  
effect.

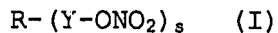
Now, it has been reported that angiotensin II receptor  
blockers have side-effects such as for example hypotension,  
hyperkalaemia, myalgia, respiratory-tract disorders, renal  
25 disorders, back pain, gastrointestinal disturbances,  
fatigue, and neutropenia (Martindale, Thirty-third edition,  
p. 921).

It was now object of the present invention to provide  
new derivatives of ARBs able not only to eliminate or at  
30 least reduce the side effects associated with their parent  
compounds, but also having an improved pharmacological  
activity. It has been so surprisingly found that  
angiotensin II receptor blocker nitroderivatives have a

significantly improved overall profile as compared to native compounds both in term of wider pharmacological activity and enhanced tolerability.

In particular, it has been recognized that the  
 5 angiotensin II receptor blocker nitroderivatives of the present invention exhibit a strong anti-inflammatory, antithrombotic and antiplatelet activity and can be furthermore employed for treating or preventing heart failure, myocardial infarction, ischemic stroke,  
 10 atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy, liver fibrosis, portal hypertension and metabolic syndromes.

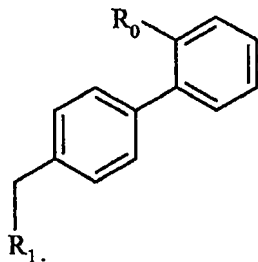
15 Object of the present invention are, therefore, Angiotensin II Receptor Blocker nitroderivatives of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof:



20 wherein:

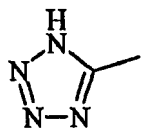
s is an integer equal to 1 or 2;

R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



25 (II)

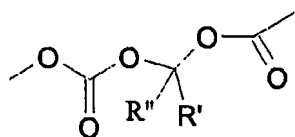
wherein:



R<sub>0</sub> is

or -N<sub>0</sub> which is a group capable to bind to Y, having one of the following meaning:

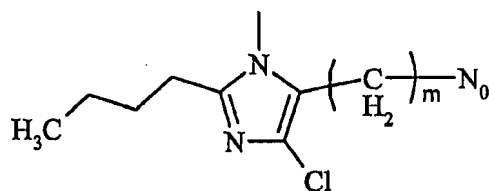
-COO-, -O-, -CONH-, -OCO-, -OCOO- or



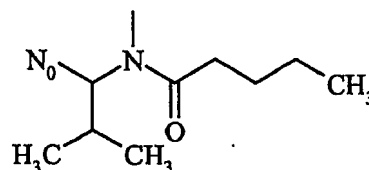
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wherein R' and R'' are the same or different, and are H or straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

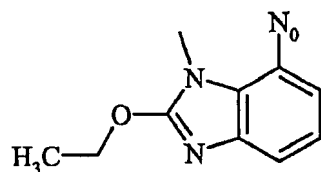
R<sub>1</sub> is selected from the group consisting of:



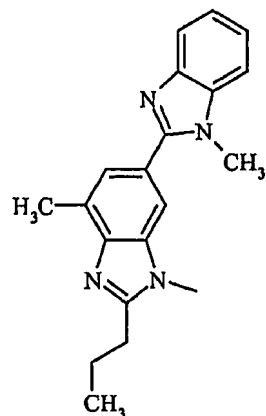
(IIa)



(IIb)

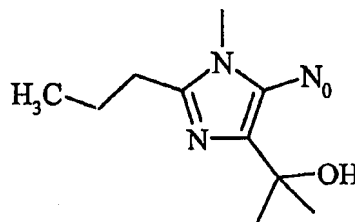


(IIc)



(IIId)

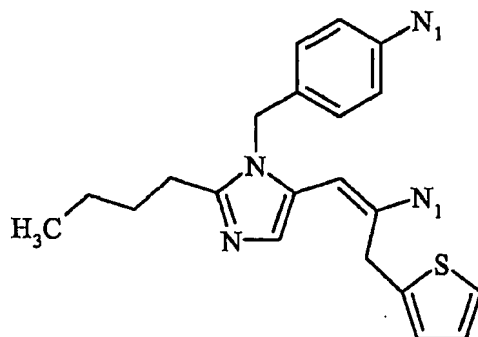
or



(IIe)



wherein  $m$  is an integer equal to 0 or 1 and  $N_0$  is as above defined;

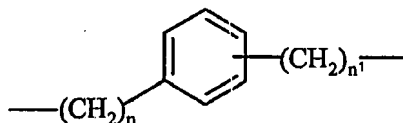


(III)

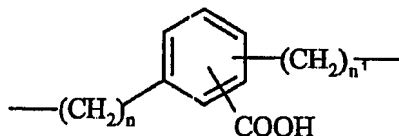
- 5 wherein  $N_1$  has the same meaning as  $N_0$  or is equal to  $-COOH$ ; with the proviso that at least one of the groups  $N_1$  is equal to  $-COO-$  or  $-CONH-$ , i.e. it is a group capable to bind to Y;

Y is a bivalent radical having the following meaning:

- 10 a)  
 - straight or branched  $C_1$ - $C_{20}$  alkylene, preferably  $C_1$ - $C_{10}$ , being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy,  $-ONO_2$  or  $T_0$ , wherein  $T_0$  is  
 15  $-OC(O)(C_1-C_{10} \text{ alkyl})-ONO_2$  or  $-O(C_1-C_{10} \text{ alkyl})-ONO_2$ ;  
 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably  $CH_3$ ;  
 20 b)

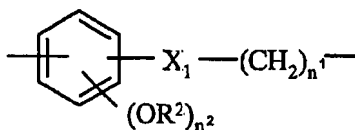


c)



wherein  $n$  is an integer from 0 to 20, and  $n^1$  is an integer from 1 to 20;

d)



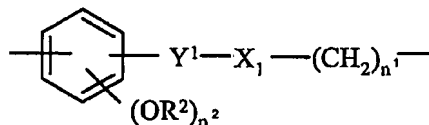
5

wherein:

$n^1$  is as defined above and  $n^2$  is an integer from 0 to 2;

$X_1 = -OCO-$  or  $-COO-$  and  $R^2$  is H or  $CH_3$ ;

e)



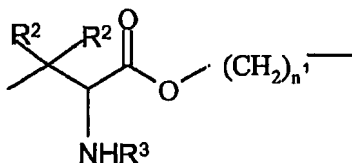
10

wherein:

$n^1$ ,  $n^2$ ,  $R^2$  and  $X_1$  are as defined above;

$Y^1$  is  $-CH_2-CH_2-$  or  $-CH=CH-(CH_2)n^2-$ ;

f)



15

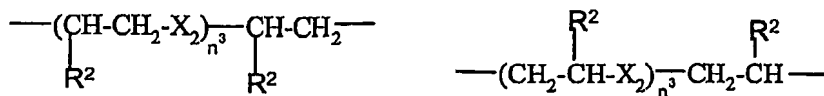
wherein:

$n^1$  and  $R^2$  are as defined above,  $R^3$  is H or  $-COCH_3$ ;

with the proviso that when  $Y$  is selected from the bivalent radicals mentioned under b)-f), the  $-ONO_2$  group is linked to a  $-(CH_2)n^1$  group;

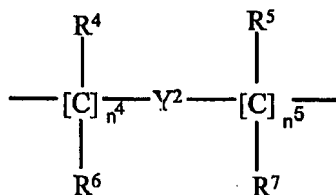
20

g)



wherein  $X_2$  is  $-O-$  or  $-S-$ ,  $n^3$  is an integer from 1 to 6, preferably from 1 to 4,  $R^2$  is as defined above;

h)



5 wherein:

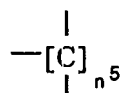
$n^4$  is an integer from 0 to 10;

$n^5$  is an integer from 1 to 10;

$R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  are the same or different, and are H or straight or branched  $C_1$ - $C_4$  alkyl, preferably  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$

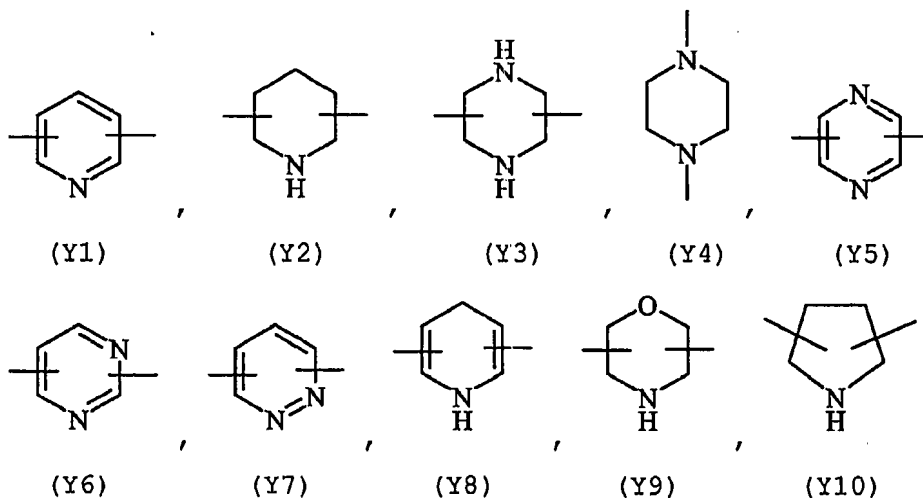
10 are H;

wherein the  $-ONO_2$  group is linked to

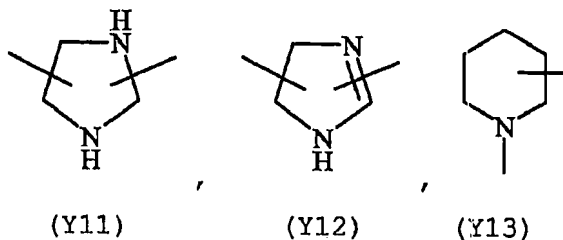


wherein  $n^5$  is as defined above;

$Y^2$  is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from



20



The term "C<sub>1</sub>-C<sub>20</sub> alkylene" as used herein refers to  
 5    branched or straight chain C<sub>1</sub>-C<sub>20</sub> hydrocarbon, preferably  
 having from 1 to 10 carbon atoms such as methylene,  
 ethylene, propylene, isopropylene, n-butylene, pentylene,  
 n-hexylene and the like.

The term "C<sub>1</sub>-C<sub>10</sub> alkyl" as used herein refers to  
 10    branched or straight chain alkyl groups comprising one to  
 ten carbon atoms, including methyl, ethyl, n-propyl,  
 isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, octyl  
 and the like.

The term "cycloalkylene" as used herein refers to ring  
 15    having from 5 to 7 carbon atoms including, but not limited  
 to, cyclopentylene, cyclohexylene optionally substituted  
 with side chains such as straight or branched (C<sub>1</sub>-C<sub>10</sub>)-  
 alkyl, preferably CH<sub>3</sub>.

The term "heterocyclic" as used herein refers to  
 20    saturated, unsaturated or aromatic 5 or 6 members ring,  
 containing one or more heteroatoms selected from nitrogen,  
 oxygen, sulphur, such as for example pyridine, pyrazine,  
 pyrimidine, pyrrolidine, morpholine, imidazole and the  
 like.

25        Another aspect of the present invention provides the  
 use of the compounds of formula (I) in combination with at  
 least a compound used to treat cardiovascular disease  
 selected from the group consisting of: ACE inhibitors,  
 HMGCoA reductase inhibitors, beta-adrenergic blockers,  
 30    calcium channel blockers, diuretics, antithrombotics such

as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

Suitable ACE inhibitors, HMGCoA reductase inhibitors, 5 beta-adrenergic blockers, calcium channel blockers, antithrombotics and diuretics are described in the literature such as The Merck Index (13<sup>th</sup> edition).

Suitable nitrosated compounds are disclosed in WO 98/21193, WO 97/16405 and WO 98/09948.

10 The administration of the compounds above reported can be carried out simultaneously or successively.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compounds and/or compositions of the present 15 invention and one or more of the compounds used to treat cardiovascular diseases reported above.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

20 Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic 25 amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran 30 with the corresponding organic or inorganic acids.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of inorganic acids

are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

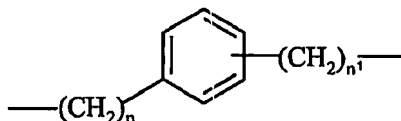
Preferred compounds are those of formula (I) wherein: s and R are as above defined;

Y is a bivalent radical having the following meaning:

a)

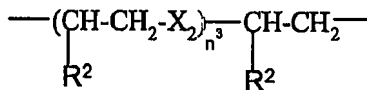
- straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene, being optionally substituted with T<sub>0</sub>, wherein T<sub>0</sub> is as above defined;

b)



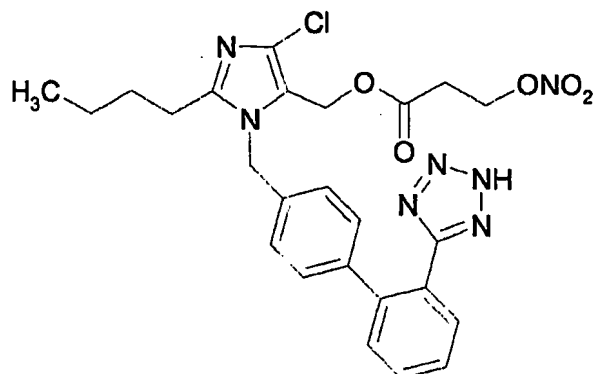
wherein n is an integer equal to 0 or 1, and n<sup>1</sup> is an integer equal to 1; with the proviso the -ONO<sub>2</sub> group is linked to a -(CH<sub>2</sub>)<sub>n</sub><sup>1</sup> group;

g)

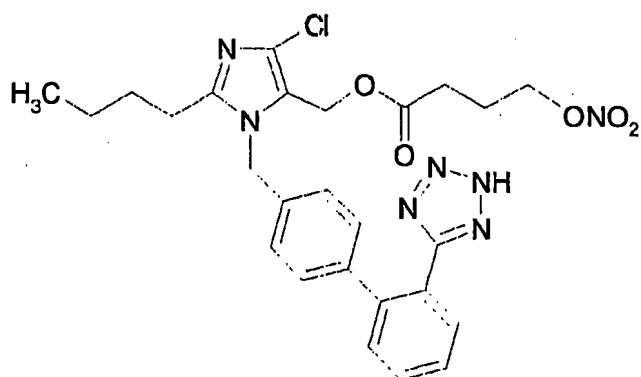


wherein X<sub>2</sub> is -O- or -S-, n<sup>3</sup> is an integer equal to 1 and R<sup>2</sup> is H;

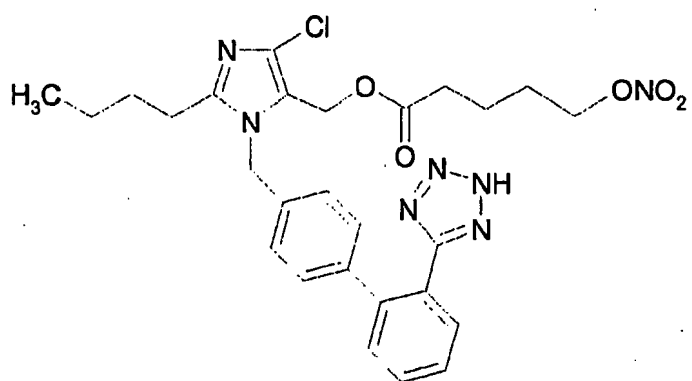
The following are preferred compounds according to the present invention:



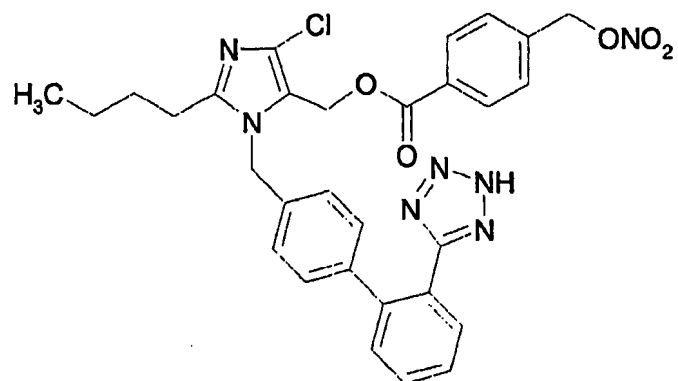
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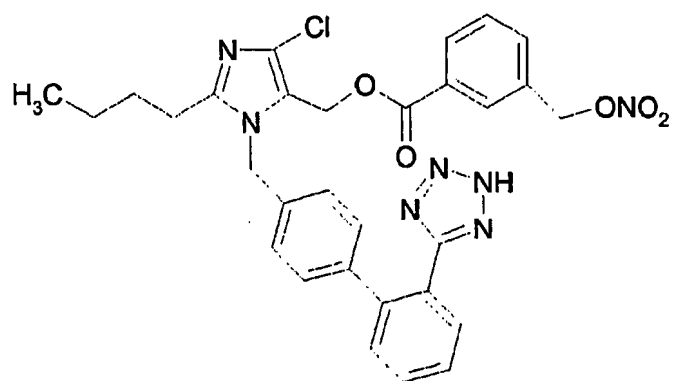
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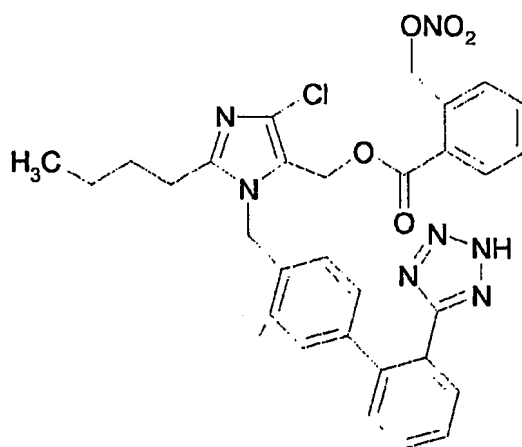
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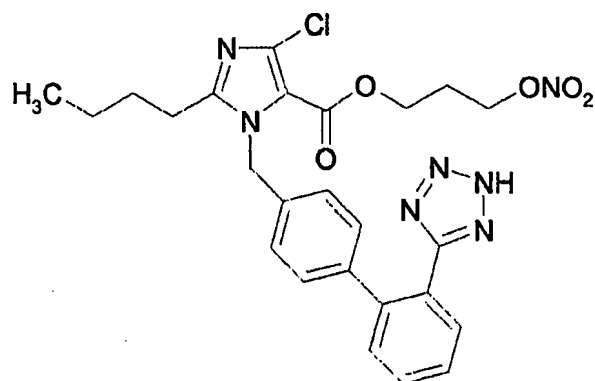


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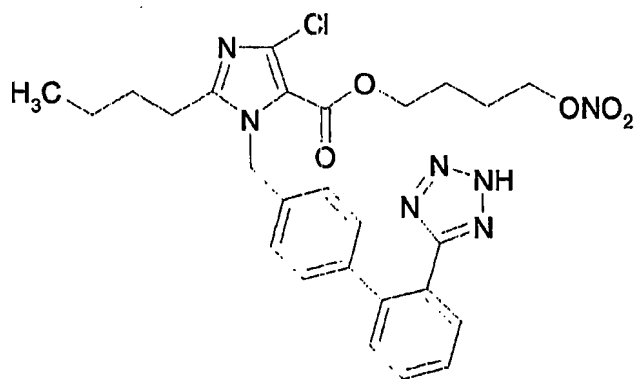


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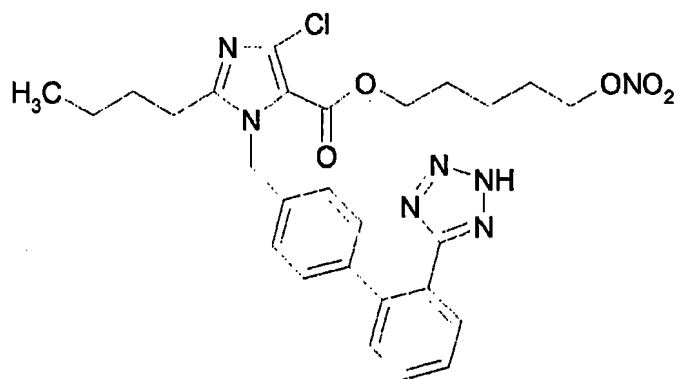




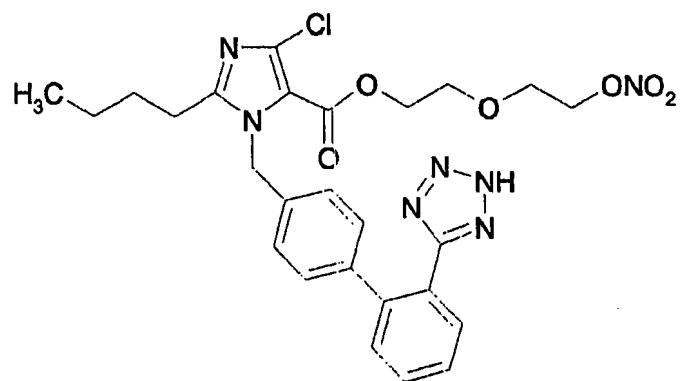
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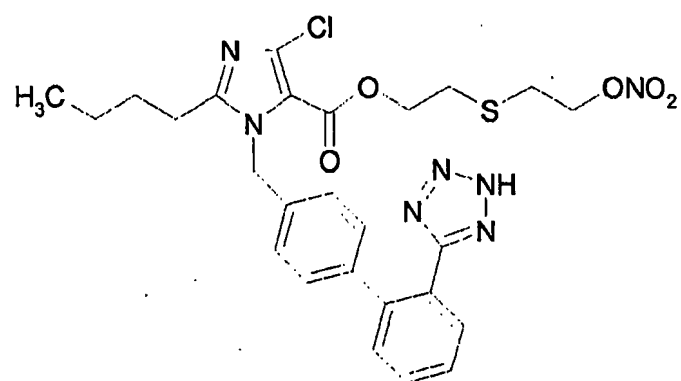
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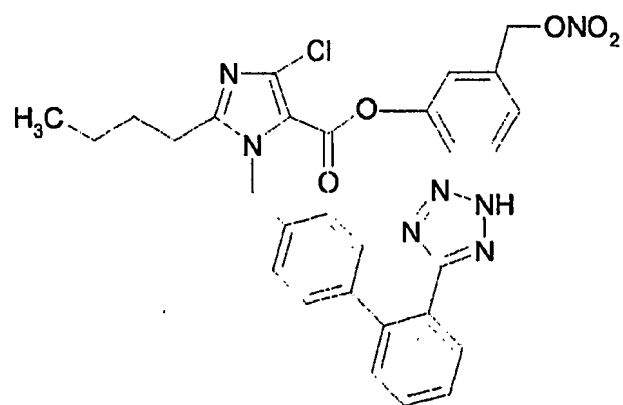
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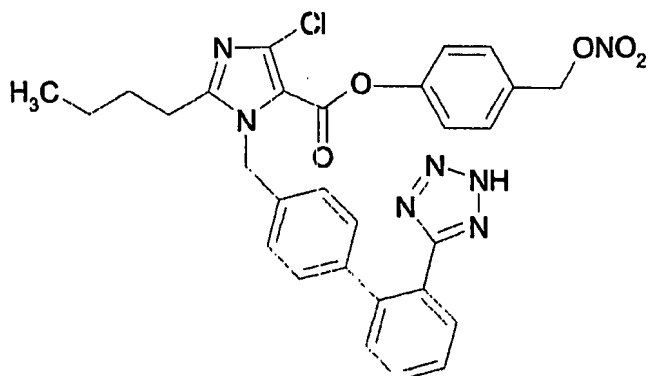
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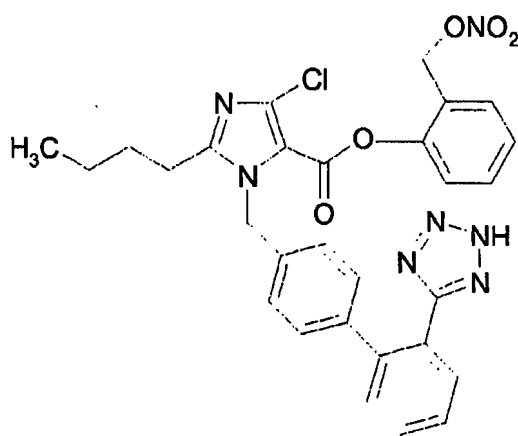
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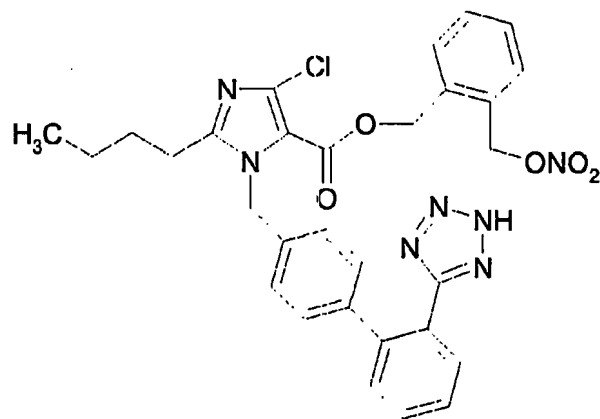
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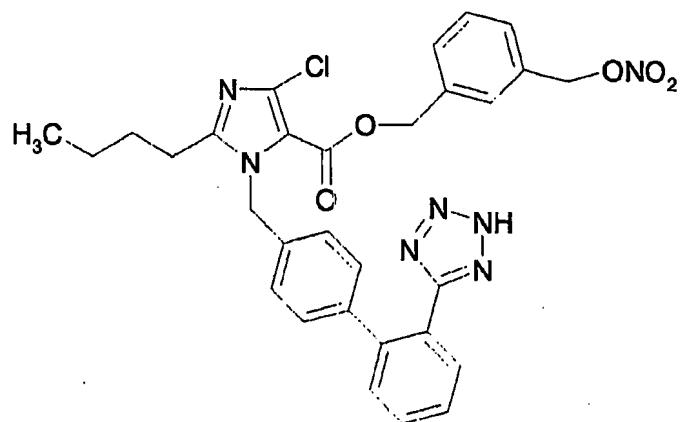
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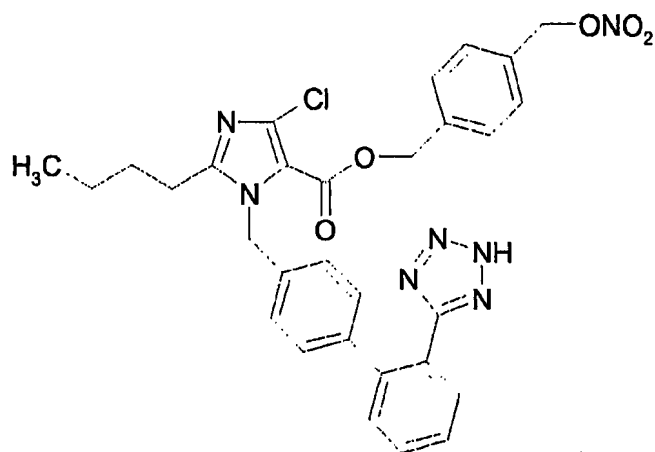
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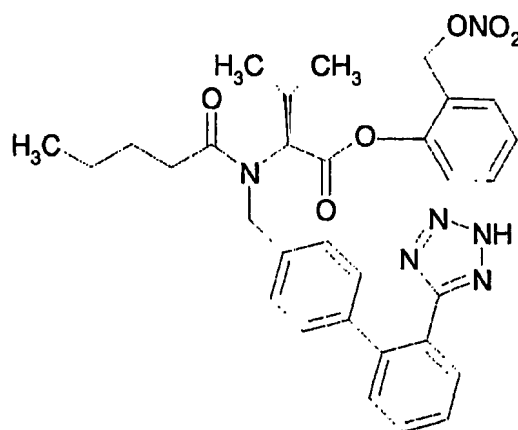
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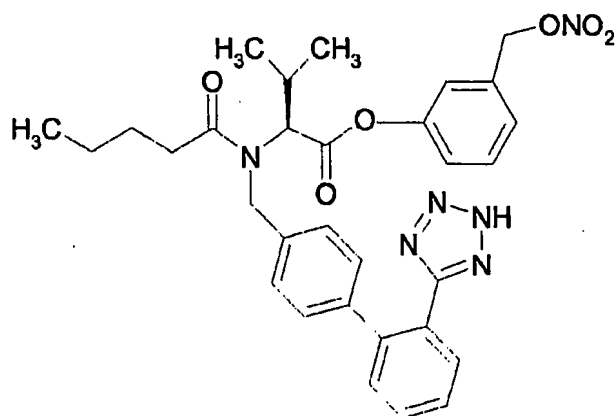
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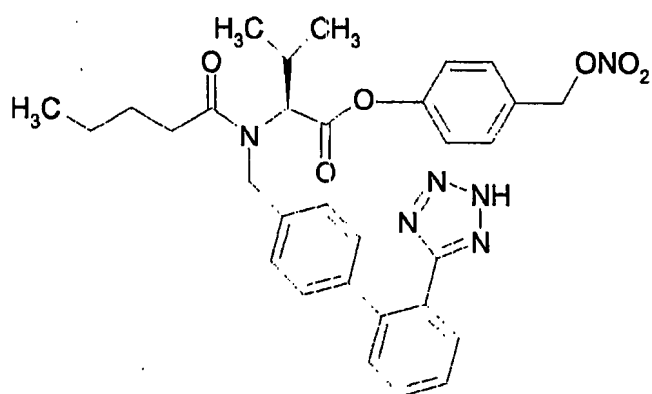
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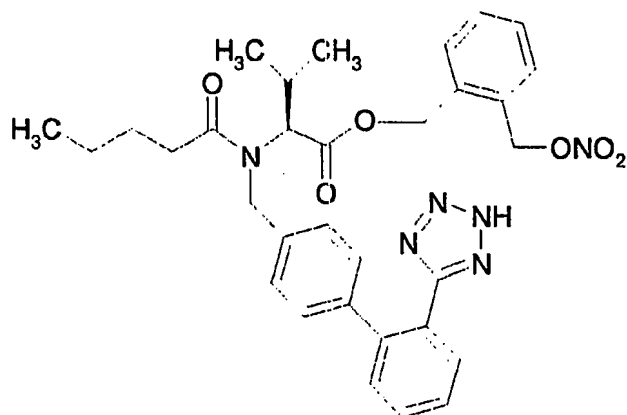
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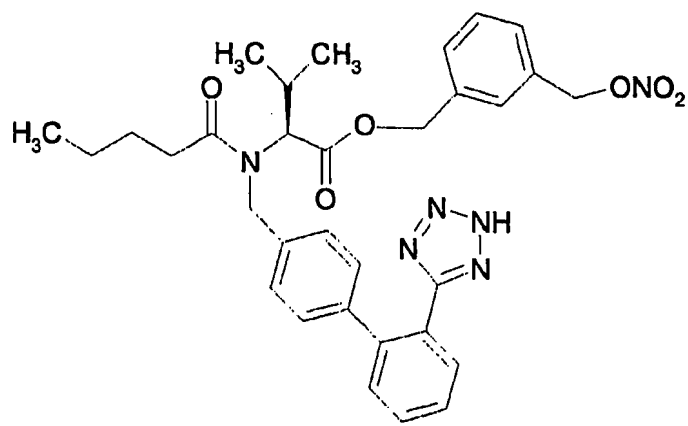
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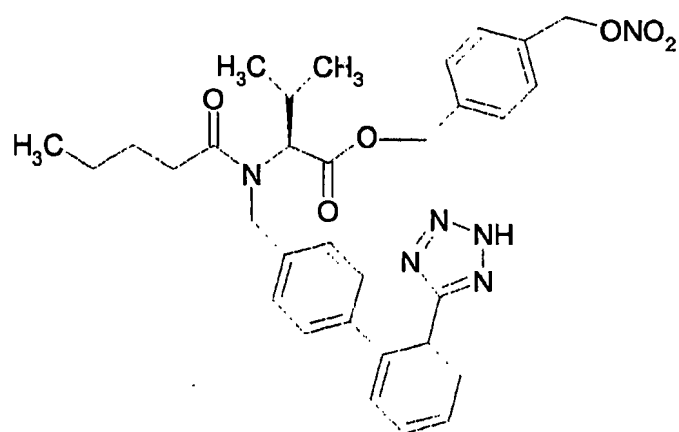
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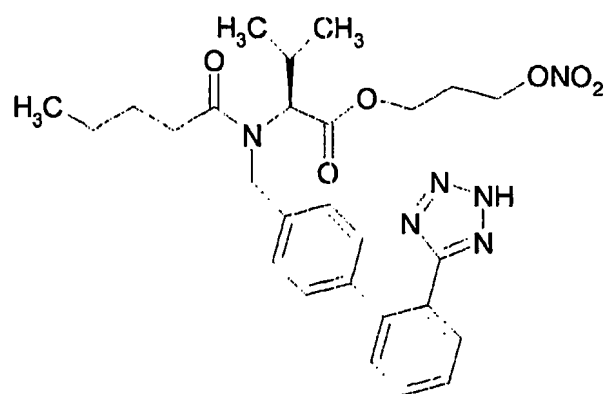
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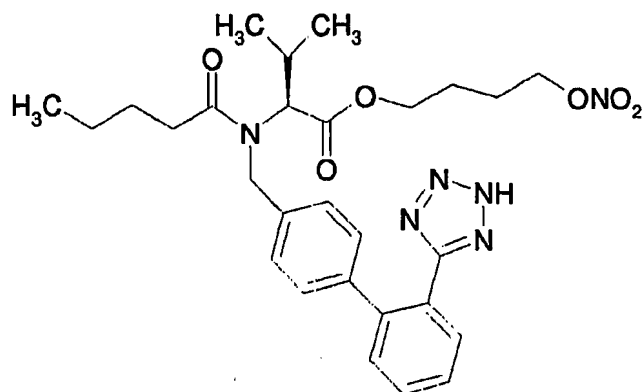
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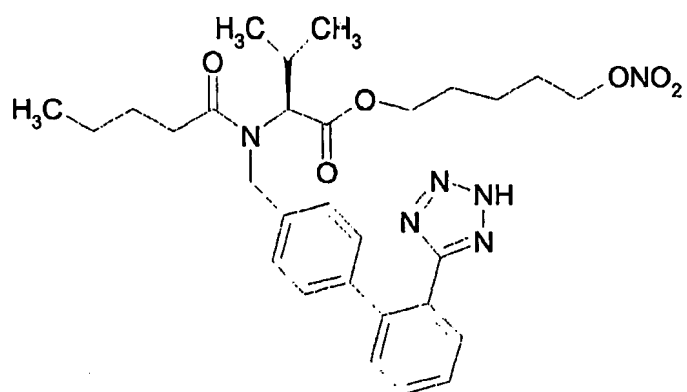
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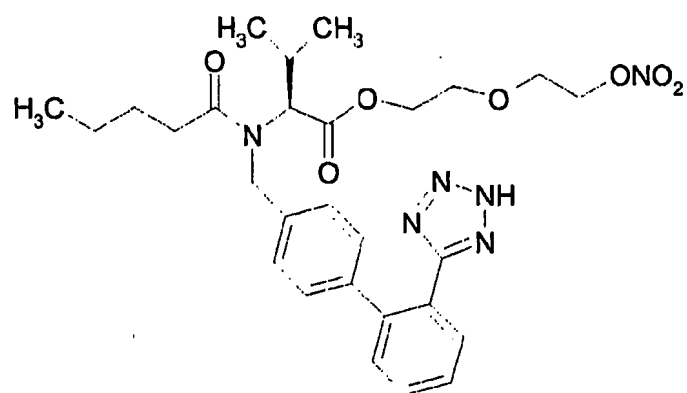
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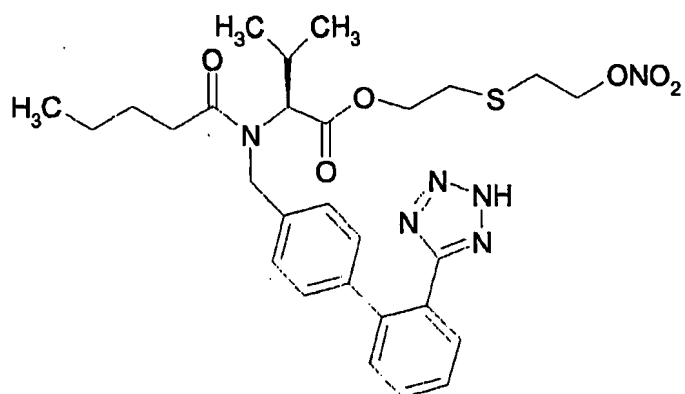
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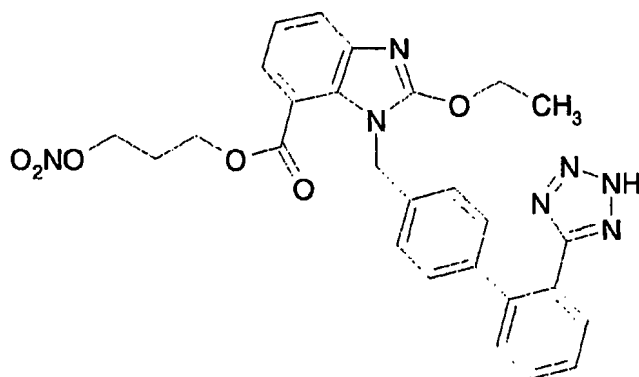
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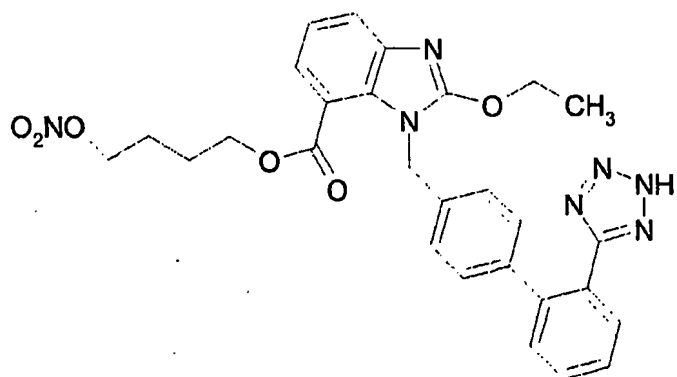
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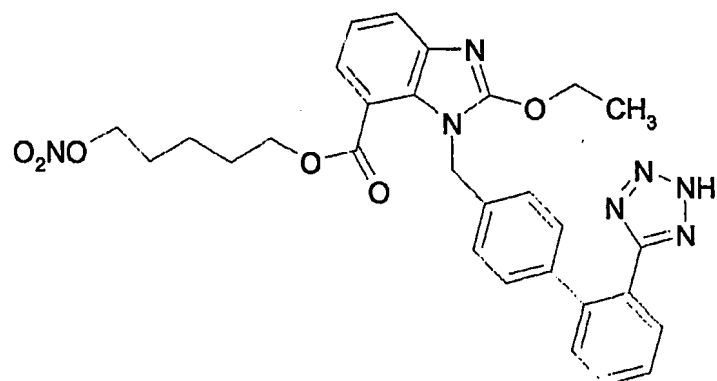


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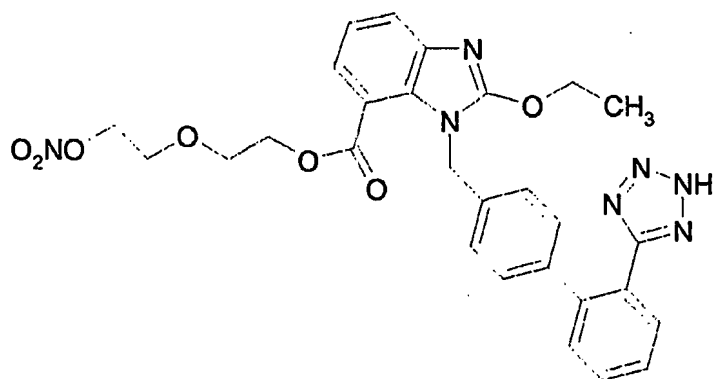


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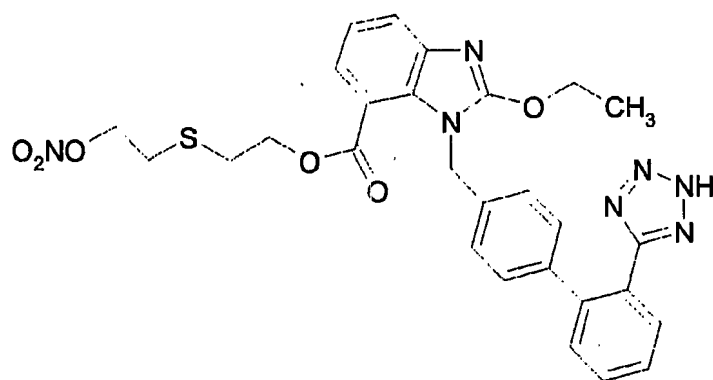




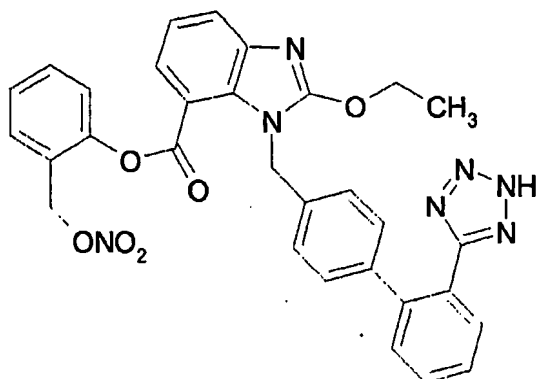
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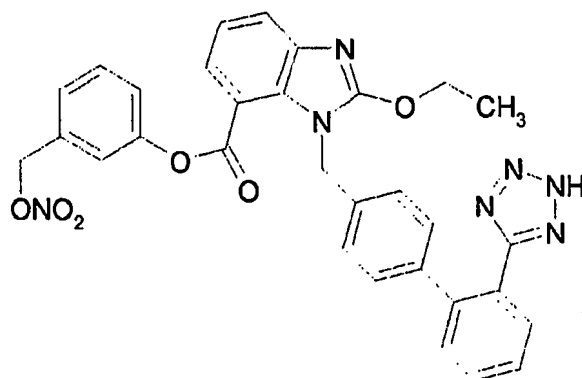
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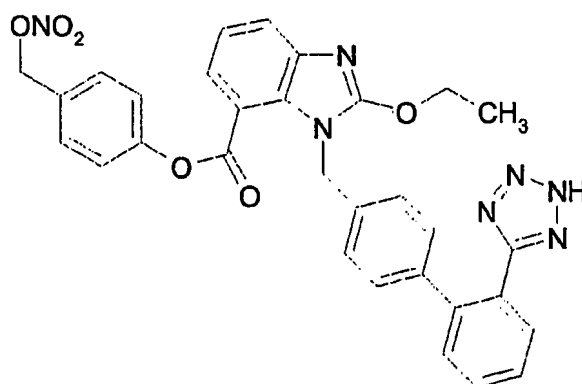
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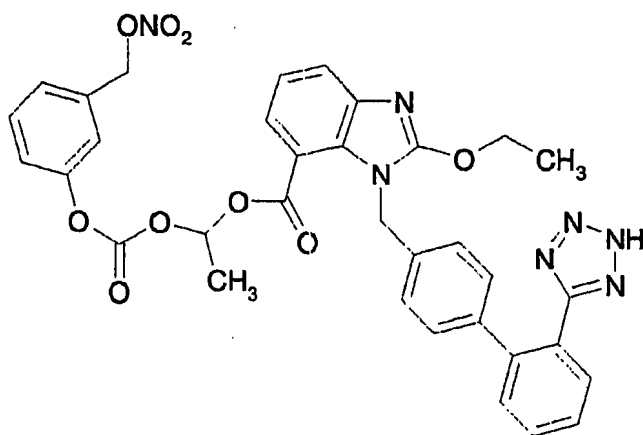
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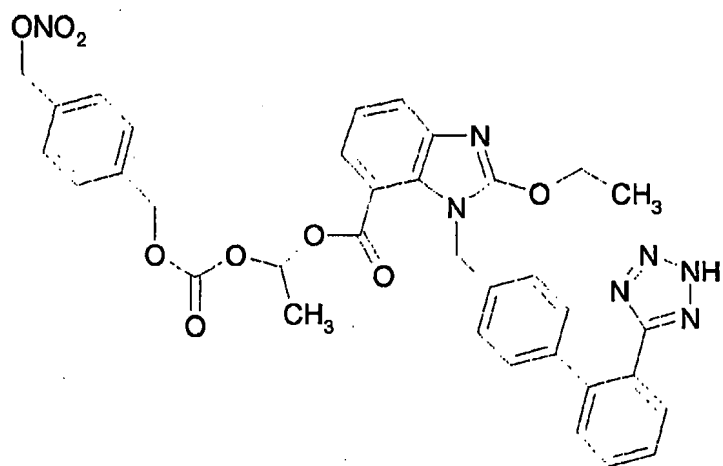
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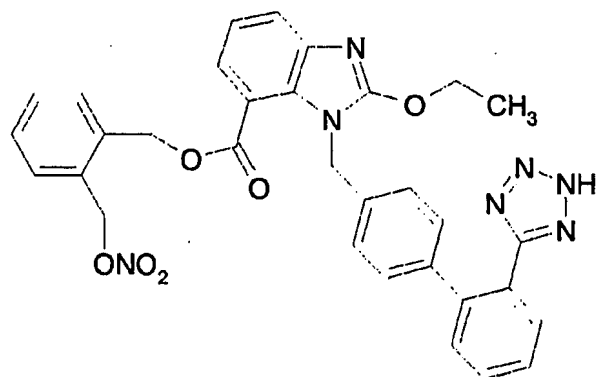
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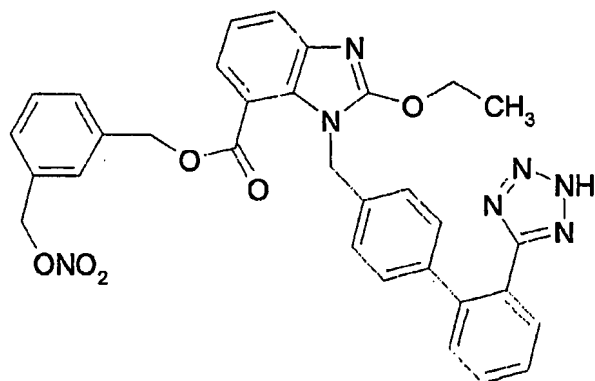
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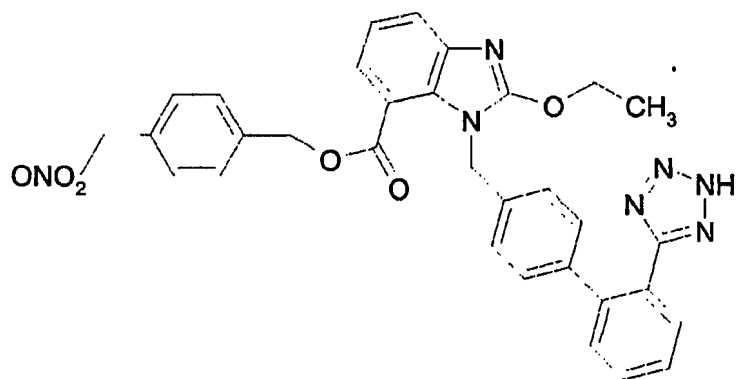
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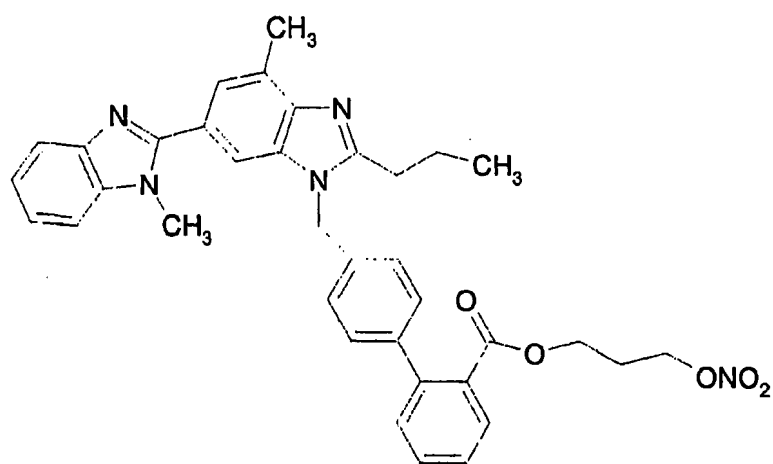
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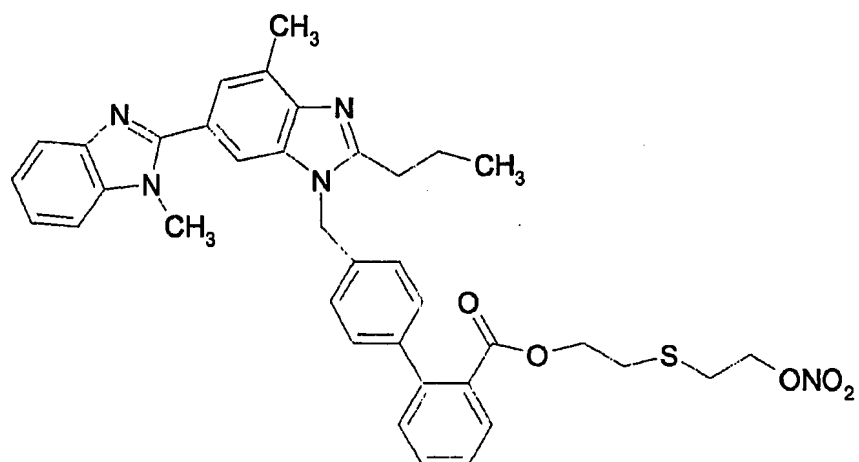


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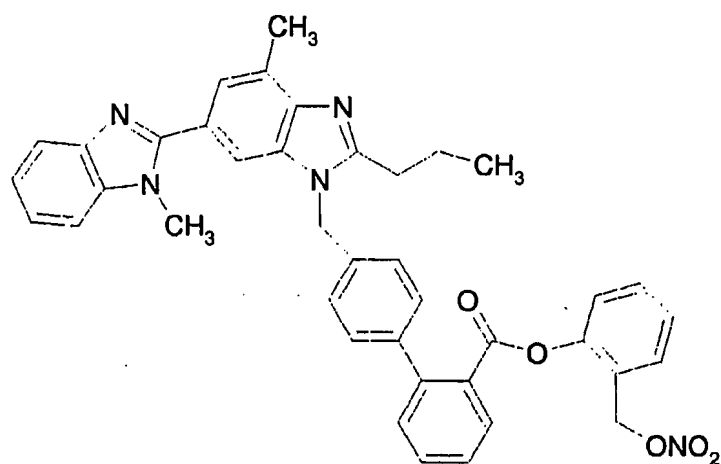


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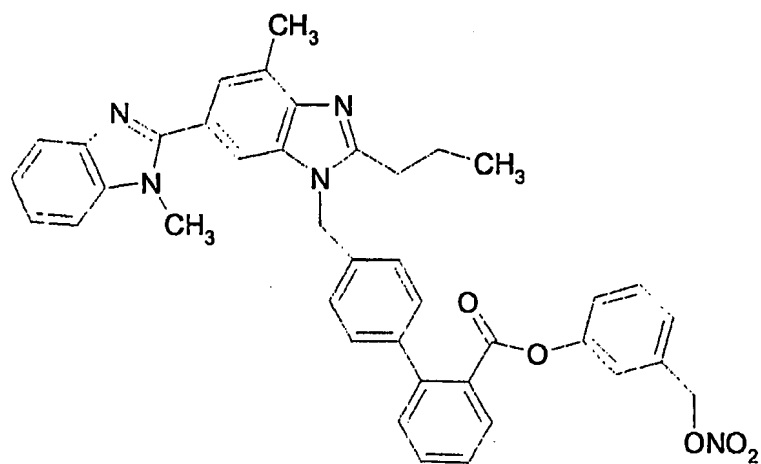




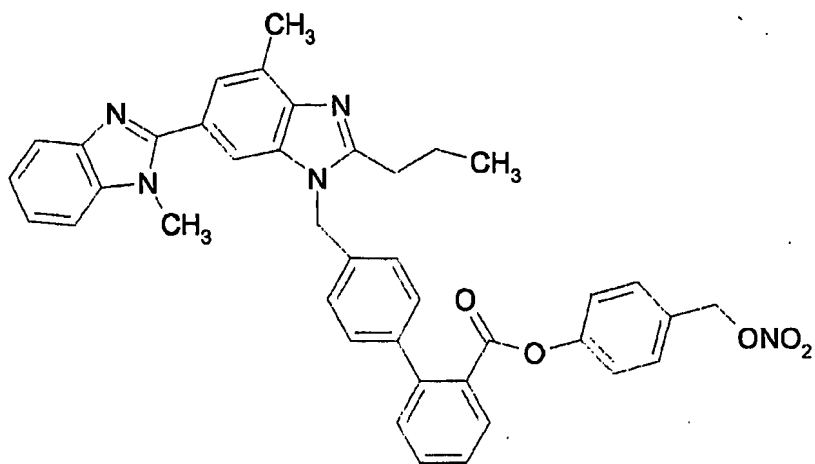
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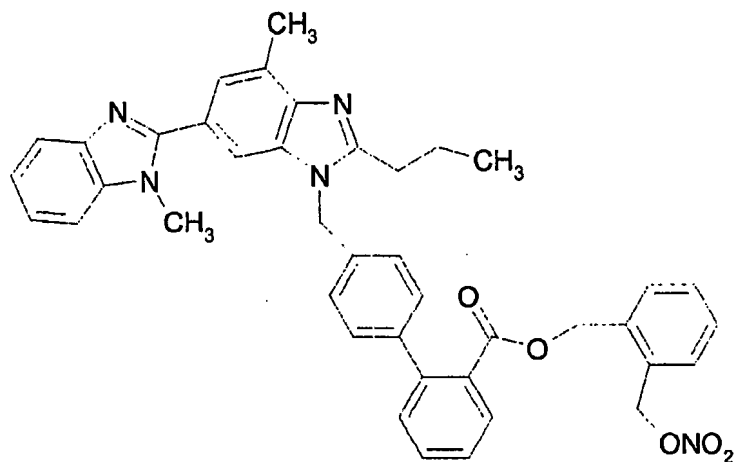
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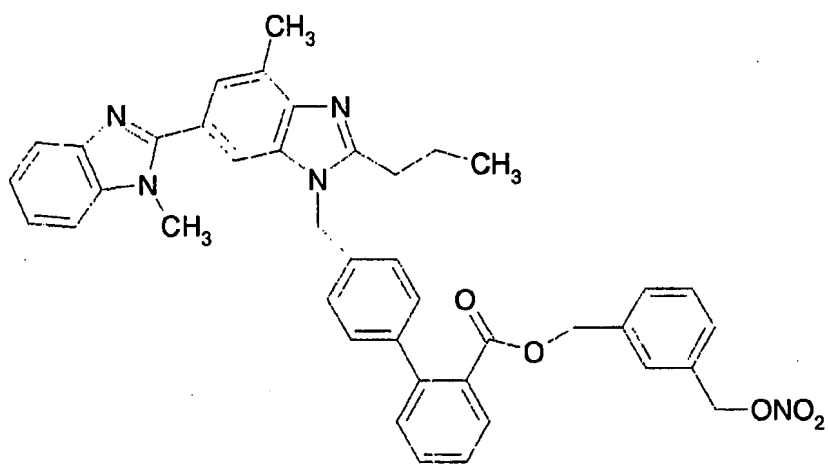
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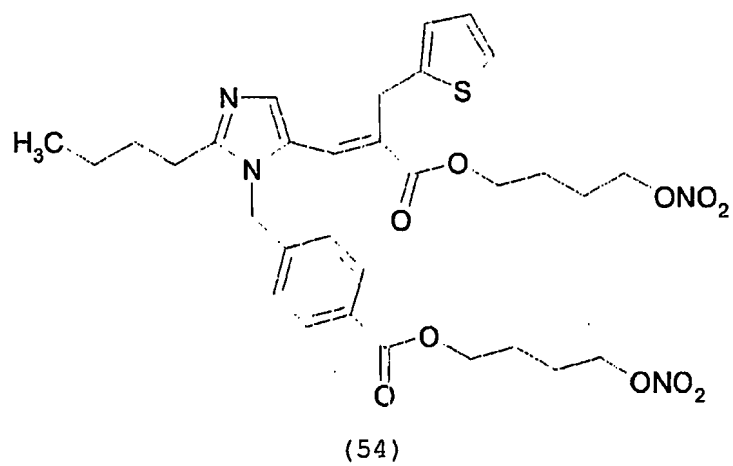
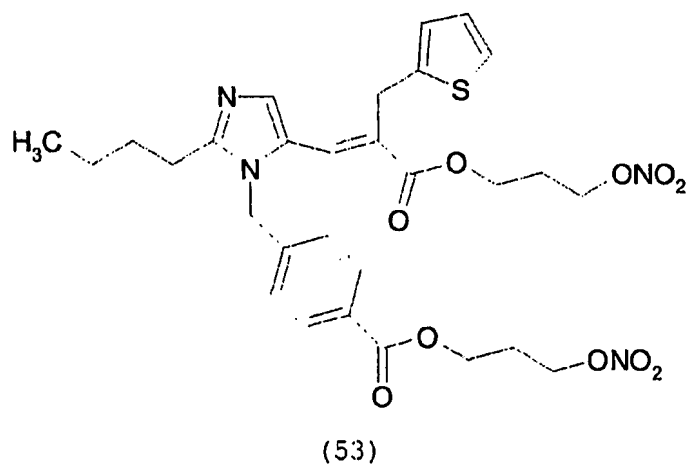
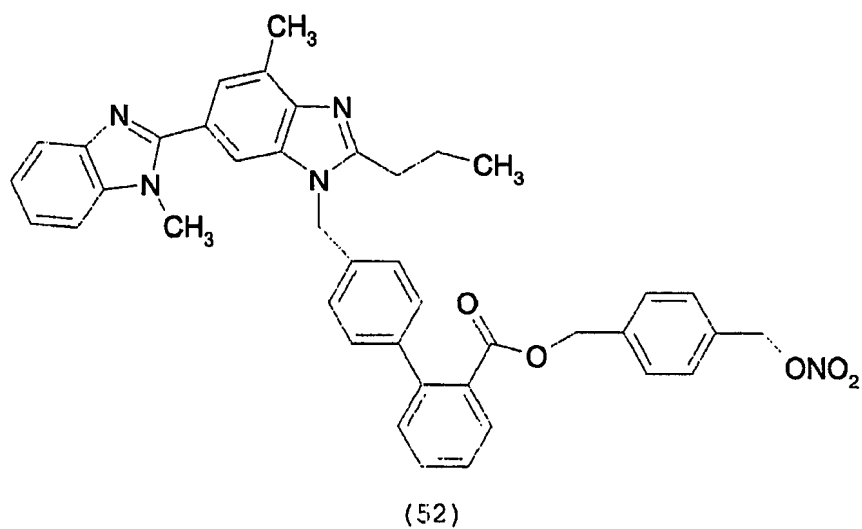
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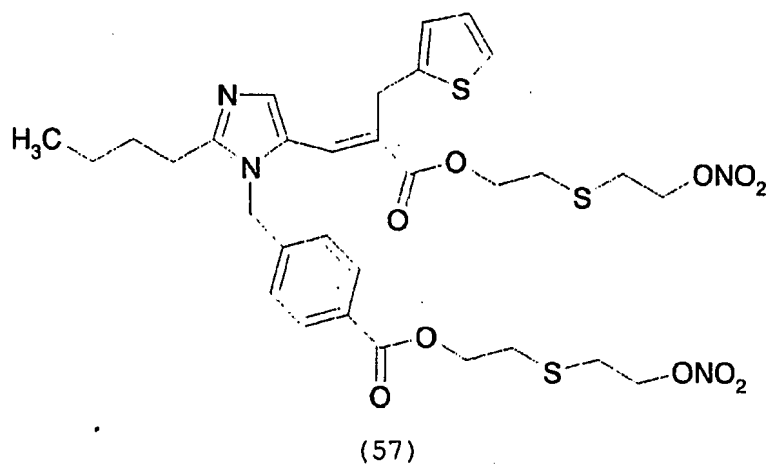
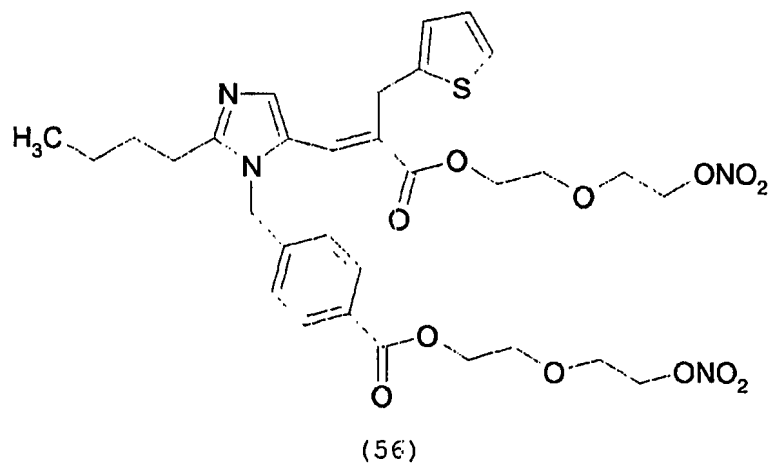
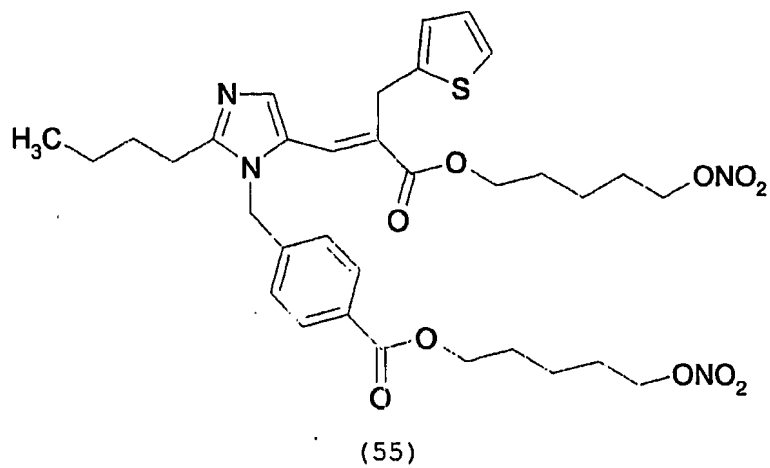
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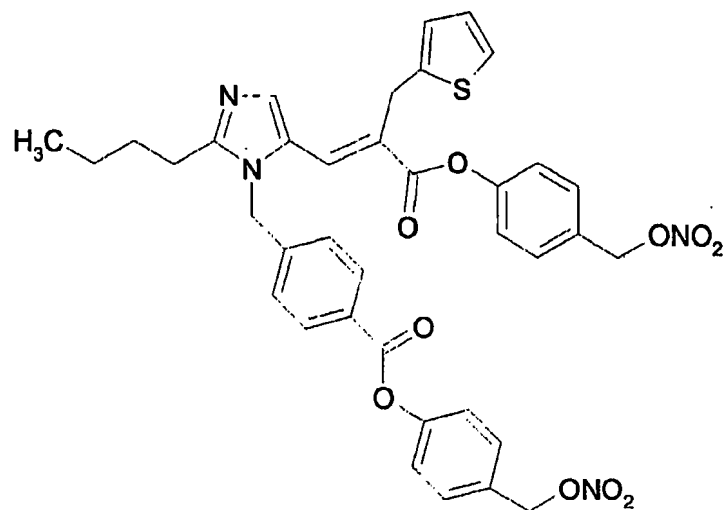
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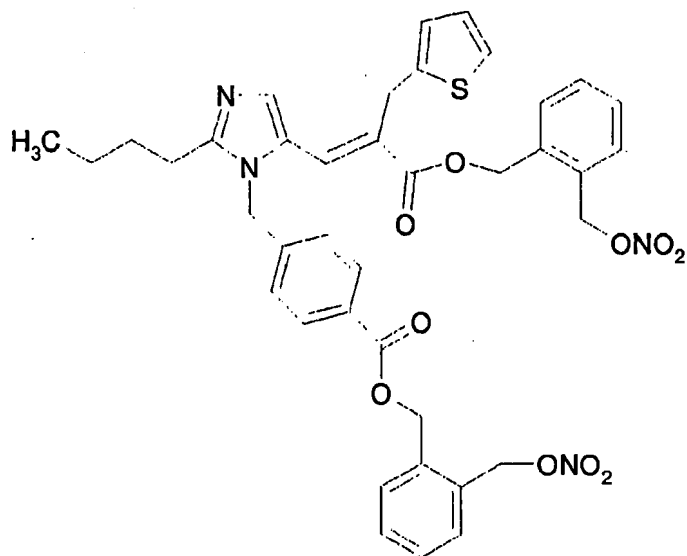




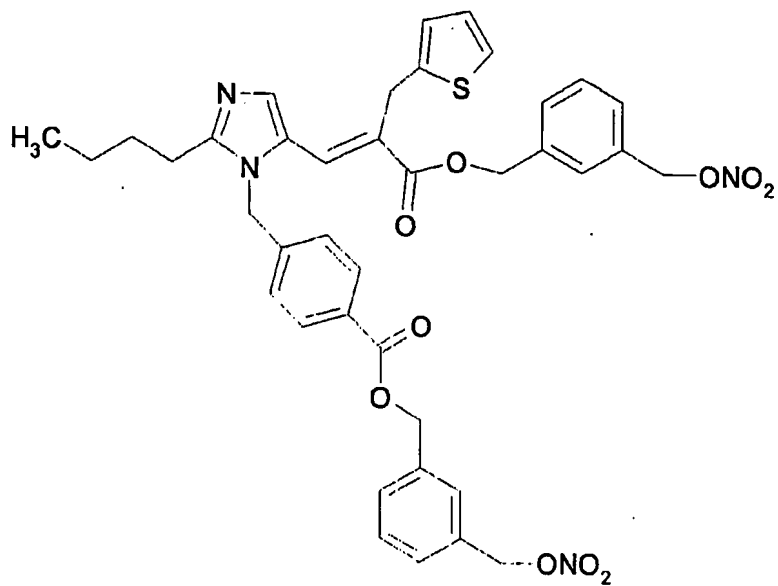




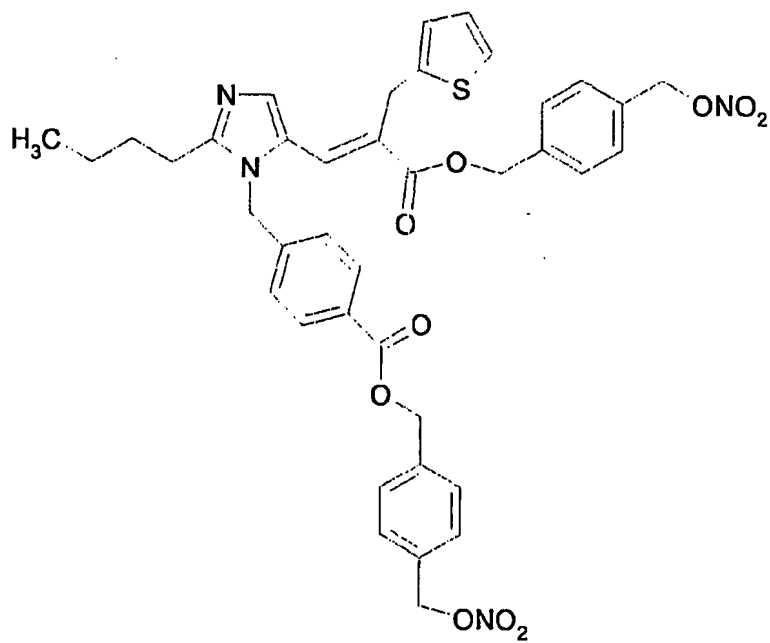
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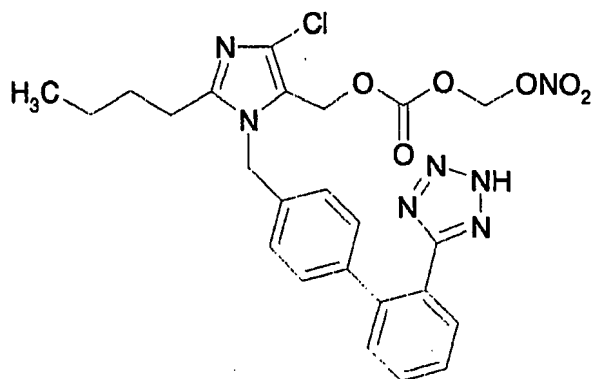
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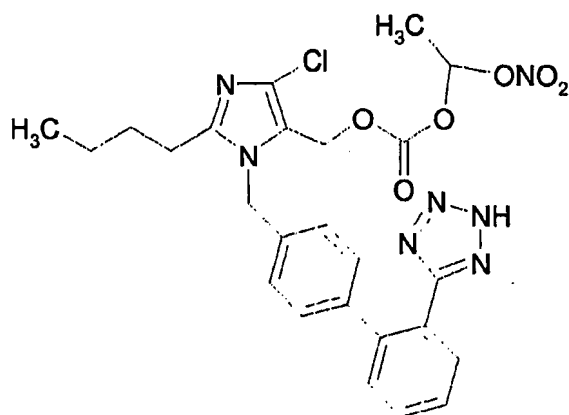
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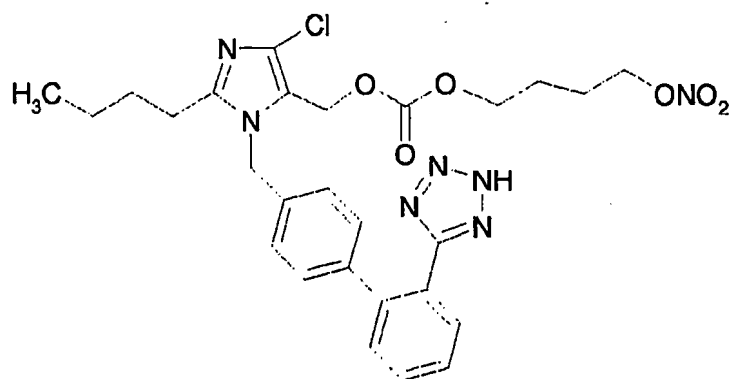
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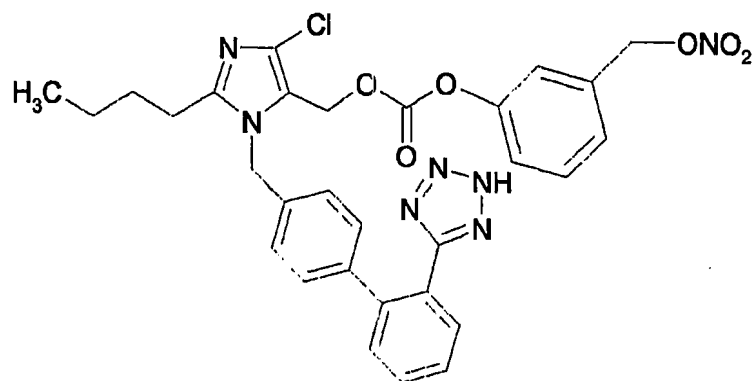
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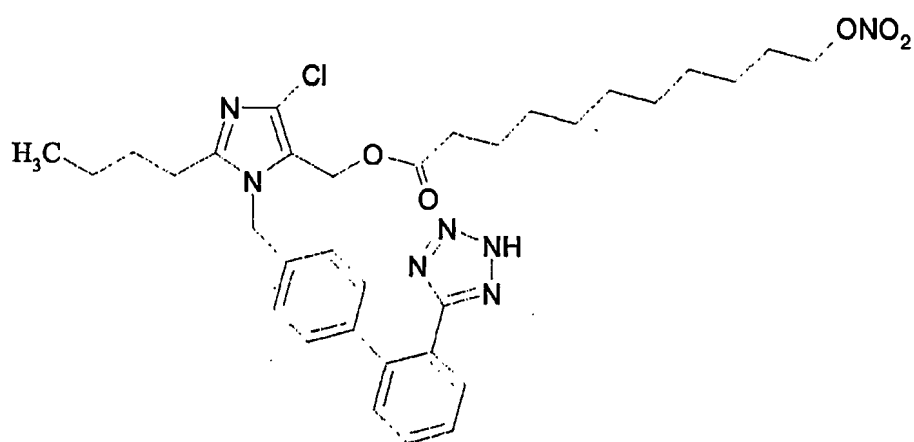
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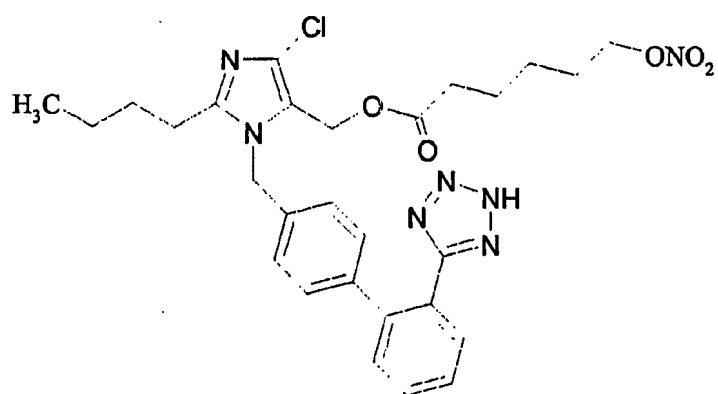


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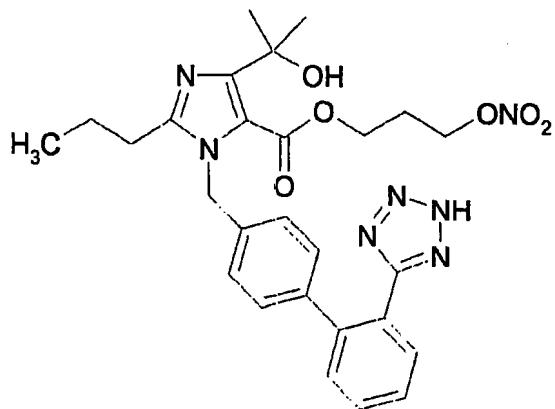


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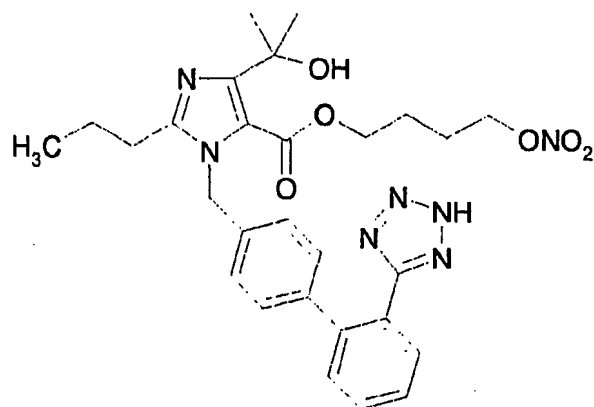
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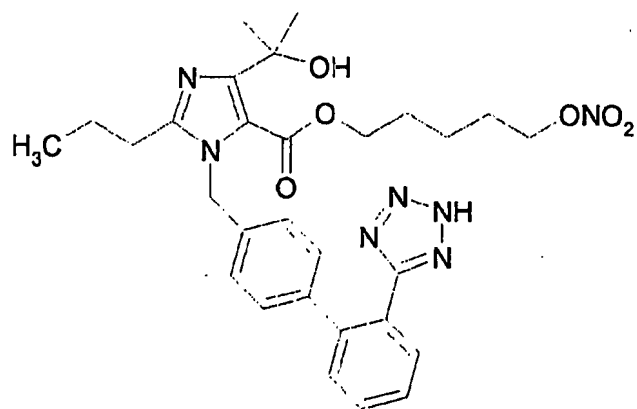


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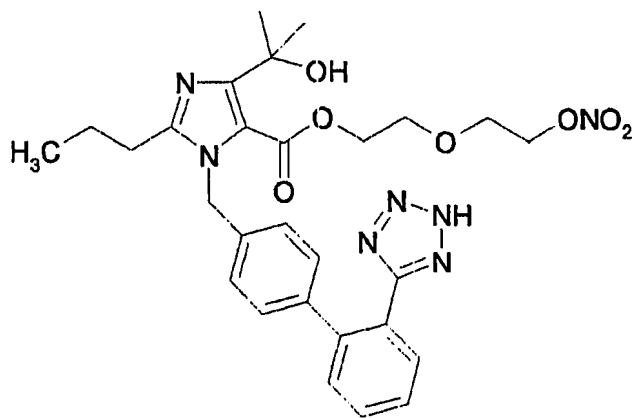


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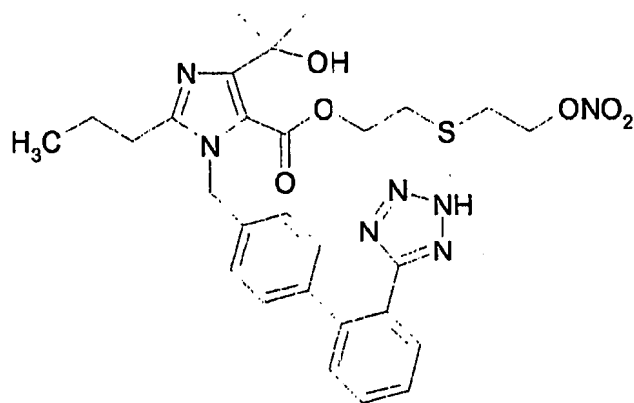
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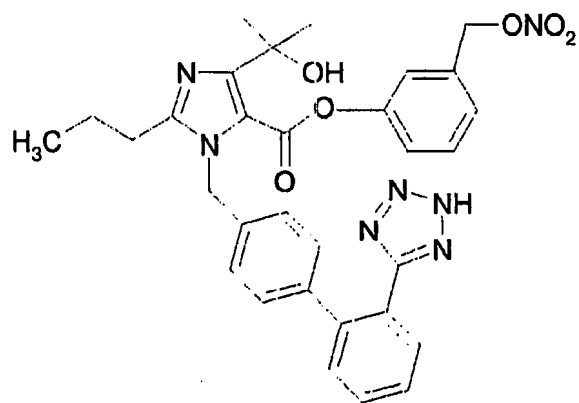


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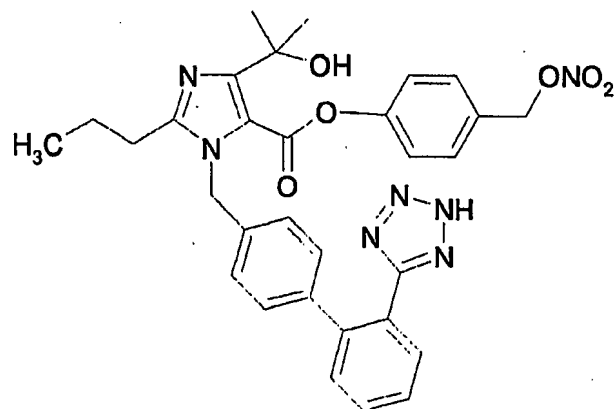
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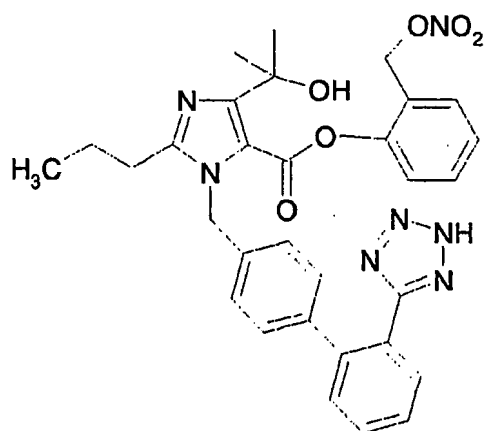


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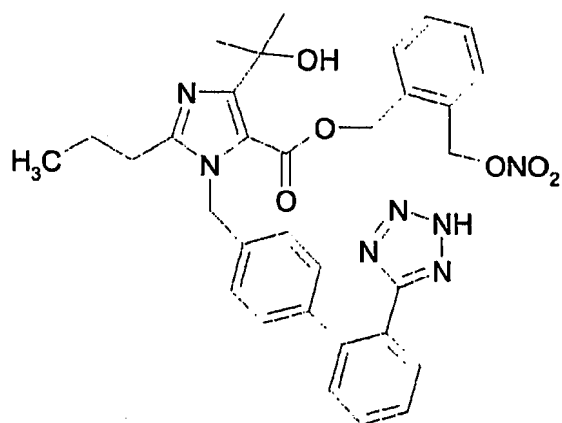




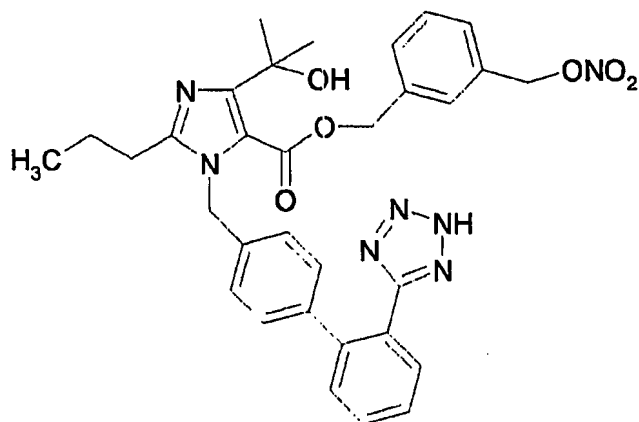
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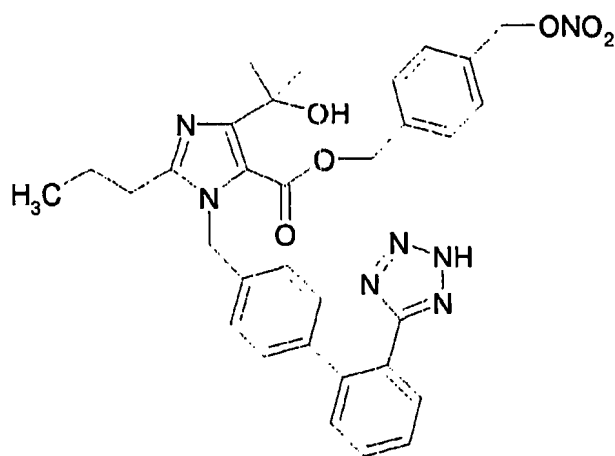
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5

As mentioned above, object of the present invention are also pharmaceutical compositions containing at least a compound of the present invention of formula (I) together with non toxic adjuvants and/or carriers usually employed in the pharmaceutical field.

The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts preferably from 50 to 500 mg. The dosage regimen and administration frequency for treating the

mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example age, body weight, sex and  
5 medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, dosage levels below or above the aforesaid range and/or more frequent may be adequate, and  
10 this logically will be within the judgment of the physician and will depend on the disease state.

The compounds of the invention may be administered orally, parenterally, rectally or topically, by inhalation or aerosol, in formulations eventually containing  
15 conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term "parenteral" as used herein, includes  
20 subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting  
25 agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride. In  
30 addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or

diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

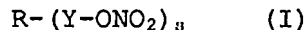
Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable  
 5 non-irritating excipient, such as cocoa butter and polyethylene glycols.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed  
 10 with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may  
 15 also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents  
 20 commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavouring and the like.

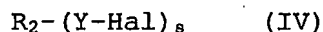
The compounds of the present invention can be synthesized  
 25 as follows.

A) The compound of general formula (I) or a pharmaceutically acceptable salt, as above defined:

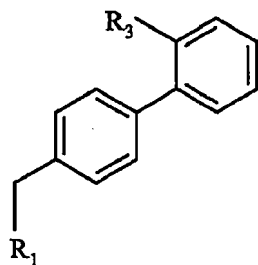


when R is the residue of formula (II), can be obtained by a  
 30 process comprising:

i) reacting a compound of formula (IV):

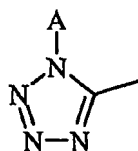


wherein  $s = 1$  and  $R_2$  is the residue of formula (IIA):



(IIA)

wherein R<sub>3</sub> is the group of formula (VA):



5 (VA)

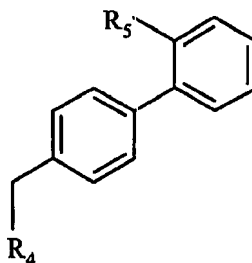
wherein A = H or W, W being a tetrazole protecting group such as trityl, tert-butoxycarbonyl (BOC) and ethyloxycarbonyl or R<sub>3</sub> is -COO-, a group capable to bind Y; R<sub>1</sub> is selected from the groups (IIa)-(IIe), as above defined, wherein N<sub>0</sub> is a group capable to bind Y; Y is as above defined and Hal is an halogen atom preferably Cl, Br or I;

with AgNO<sub>3</sub> in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20°-80°C; alternatively the reaction with AgNO<sub>3</sub> can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between 100-180°C for short time (1-60 min) and

20 ii) optionally acid hydrolysing the tetrazole protecting group W, as well known in the art, for example as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980 and

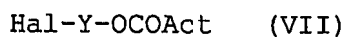
iii) if desired, converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

- The compound of formula (IV) can be obtained by reacting a compound of formula (V):

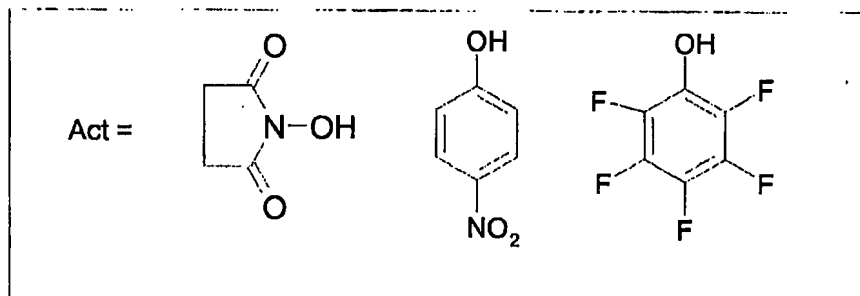


(V)

- 5 wherein  $R_5$  is the group of formula (VA) as above defined or  $-\text{COOH}$  and  $R_4$  has the same meaning as  $R_1$  with  $N_0 = -\text{COOH}$  or  $-\text{OH}$ ,  
 i.1) when  $R_5$  is the group (VA),  $R_4 = R_1$  and  $R_1$  is the group (IIa) wherein  $m = 1$  and  $N_0 = -\text{OH}$ , with a compound of  
 10 formula (VI) or (VII):

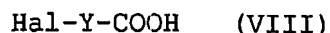


- wherein Hal and Y are as above defined and Act is Hal or a carboxylic acid activating group used in peptide chemistry  
 15 as:



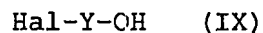
- The reaction is generally carried out in presence of a inorganic or organic base in an aprotic polar/non-polar  
 20 solvent such as DMF, THF or  $\text{CH}_2\text{Cl}_2$  at temperatures range between  $0^\circ\text{--}65^\circ\text{C}$  or in a double phase system  $\text{H}_2\text{O}/\text{Et}_2\text{O}$  at temperatures range between  $20^\circ\text{--}40^\circ\text{C}$ ;

The compounds of formula (VI) where Act is = Hal are commercially available or can be obtained from the corresponding acids of formula (VIII):



- 5 by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of  $\text{P}^{\text{III}}$  or  $\text{P}^{\text{V}}$  in solvents inert such as toluene, chloroform, DMF, etc. The corresponding acids are commercially available compounds. The compounds of formula (VI) where Act is not Hal can be  
10 obtained from the corresponding compounds of formula (VI) where Act is Hal by reacting with N-Hydroxysuccinimide or with the appropriate substituted phenols in the presence of a base as known in the literature.

- The compounds of formula (VII) where Act is = Hal are  
15 commercially available or can be obtained from the corresponding alcohols of formula (IX):



- by reaction with triphosgene in presence of an organic base; the compounds of formula (VII) where Act is not = Hal  
20 can be obtained from the corresponding compound (VII) where Act is Hal by reacting with N-Hydroxysuccinimide or with the appropriate substituted phenols in the presence of a base as known in the literature.

- Alternatively, the compound of formula (IV) can be obtained  
25 by reacting a compound of formula (V) as defined in i.1), with a compound of formula (VIII), as above defined and commercially available, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC), EDAC in the presence of a catalytic amount of DMAP or activating agent as N,N'-carbonyldiimidazole (CDI) in solvent such as DMF, THF,  
30 chloroform at a temperature in the range from  $-5^{\circ}\text{C}$  to  $50^{\circ}\text{C}$ ; i.2) when  $\text{R}_5$  is the group (VA) or  $-\text{COOH}$ ,  $\text{R}_4 = \text{R}_1$  and  $\text{R}_1$  is selected from the groups (IIa)-(IIId) wherein  $m = 0$  and  $\text{N}_0 =$

-COOH, with a compound of formula (IX), as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC), EDAC in the presence of a catalytic amount of DMAP or activating the carboxylic group with agent as N,N'-carbonyldiimidazole (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

The compounds of formula (IX) are commercially available. Alternatively, transforming the group -COOH into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as DMF, THF or CH<sub>2</sub>Cl<sub>2</sub> at temperatures range between 0°-65°C or in a double phase system H<sub>2</sub>O/Et<sub>2</sub>O at temperatures range between 20°- 40°C;

A1) Alternatively, the compounds of formula (I) as above defined, when R is the residue of formula (II), can be obtained by reacting compounds of formula (V) as above defined:

i.1.1) when R<sub>5</sub> is the group (VA), R<sub>4</sub> = R<sub>1</sub> and R<sub>1</sub> is the group (IIa) wherein m = 1 and N<sub>0</sub> = -OH, with a compound of formula (X):



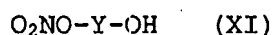
where Y is as previously defined and Z is OH or the group Act already defined, with the best suitable synthetic path, for example in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or EDAC or activating with N,N'-carbonyldiimidazole (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C and/or in the presence of a organic or inorganic base.

The compounds of formula (X) can be obtained from the corresponding alcohols by reaction with nitric acid and



acetic anhydride in a temperature range from  $-50^{\circ}\text{C}$  to  $0^{\circ}\text{C}$  or reacting the corresponding halogen derivatives of formula (VI) or (VIII) with  $\text{AgNO}_3$  as already described.

1.2.1) when  $\text{R}_5$  is the group (VA) or  $-\text{COOH}$ ,  $\text{R}_4 = \text{R}_1$  and  $\text{R}_1$  is  
 5 selected from the groups (IIa)-(IId) wherein  $m = 0$  and  $\text{N}_0 = -\text{COOH}$ , with a compound of formula (XI):

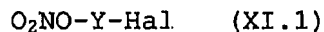


wherein Y is as above defined; in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or EDAC or an  
 10 activating agent as N,N'-carbonyldiimidazole (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from  $-5^{\circ}\text{C}$  to  $50^{\circ}\text{C}$ .

The compound of formula (XI) can be obtained by reacting a compound of formula (IX) with  $\text{AgNO}_3$  in a suitable organic  
 15 solvent such as acetonitrile or THF under nitrogen at temperatures range between  $20^{\circ}$ - $80^{\circ}\text{C}$ ;

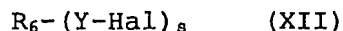
alternatively the reaction with  $\text{AgNO}_3$  can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between  $100$ - $180^{\circ}\text{C}$  for  
 20 short time (1-60 min).

Alternatively when  $\text{R}_5$  is the group (VA) or  $-\text{COOH}$ ,  $\text{R}_4 = \text{R}_1$  and  $\text{R}_1$  is selected from the groups (IIa)-(IIe) wherein  $m = 0$  and  $\text{N}_0 = -\text{COOH}$ , with a compound of formula (XI.1):



25 where Y and Hal are as previously defined by reacting in the presence of an inorganic or organic base able to salify the carboxylic group.

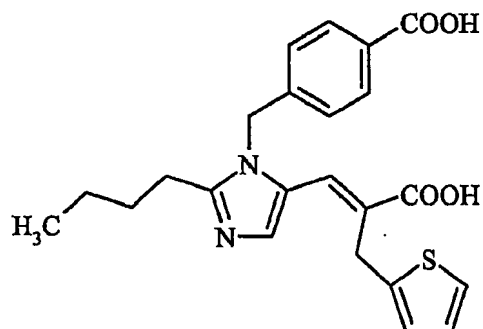
B) The compound of general formula (I), when R is the  
 30 residue of formula (III), can be obtained by reacting a compound of formula (XII):



wherein  $s = 2$ ,  $\text{R}_6$  is the residue (III) and  $\text{N}_1$  is  $-\text{COO}-$ , Y and Hal are as above defined,

with  $\text{AgNO}_3$  as already described.

Compounds of formula (XII) are obtained by reacting a compound of formula (XIII):



5

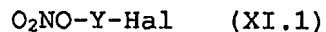
(XIII)

with compounds of formula (IX), as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or EDAC or an activating agent as  $N,N'$ -carbonyldiimidazole (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C as already described.

Alternatively, transforming the group  $-\text{COOH}$  into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as THF or  $\text{CH}_2\text{Cl}_2$  at a temperature in the range between 0°-65°C or in a double phase system.

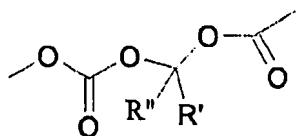
20 B1) Alternatively, the compounds of general formula (I) as above defined, when R is the residue of formula (III), can be obtained by reacting the compound of formula (XIII) with a compound of formula (XI), as above defined, in presence of a condensing or activating agent as already described.

Alternatively, transforming the group  $-\text{COOH}$  into a salt with an inorganic or organic base according to methods well known in the literature, and reacting with:

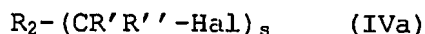


as known in the literature.

- C) The compounds of formula (I), as above defined,  
 5 when  $s = 1$  and R is the residue of formula (II), wherein  $\text{R}_0$   
 is the tetrazole group and  $\text{R}_1$  is the group (IIa) wherein  $m$   
 $= 1$  and  $\text{N}_0$  is



- 10 wherein  $\text{R}'$  and  $\text{R}''$  are as above defined,  
 can be obtained by reacting a compound of formula (IVa):



wherein  $s = 1$ ,  $\text{R}_2$  and Hal are as above defined,  $\text{R}_3$  is the  
 group (VA),  $\text{R}_1$  is the group (IIa) wherein  $m = 1$  and  $\text{N}_0$  is

- 15  $-\text{OCOO}-$ ,

with a compound of formula (X) as above defined, in  
 presence of an organic or inorganic base in a polar solvent  
 as DMF, THF, acetonitrile at a temperature in the range  
 from  $-5^\circ\text{C}$  to  $60^\circ\text{C}$  or in a double phase system as already

- 20 known in the literature.

The compounds (IVa) can be obtained by reacting a compound  
 of formula (V) as above defined, wherein  $\text{R}_5$  is the group  
 (VA),  $\text{R}_4 = \text{R}_1$  and  $\text{R}_1$  is the group (IIa) wherein  $m = 1$  and  $\text{N}_0$   
 $= -\text{OH}$ , with a compound of formula (VIIa):

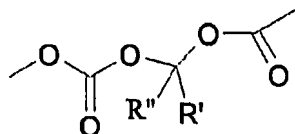
- 25  $\text{Hal}-\text{CR}'\text{R}''-\text{OCOAct} \quad (\text{VIIa})$

where Act as the same meaning above described for (VII),  
 in the same manner already described for the compounds  
 (IV); and optionally acid hydrolysing the tetrazole  
 protecting group as above described.

- 30

D) The compounds of formula (I), as above defined,  
 when  $s = 1$  and R is the residue of formula (II), wherein  $\text{R}_0$

is the tetrazole group and  $R_1$  selected from the groups (IIa)-(IIc) wherein  $m = 0$  and  $N_0$  is



wherein  $R'$  and  $R''$  are as above defined,

- 5 can be obtained by reacting a compound of formula (V), wherein  $R_5$  is the group (VA),  $R_4 = R_1$  and  $R_1$  is the group (IIc) wherein  $N_0 = -COOH$ , with a compound of formula (XIV):



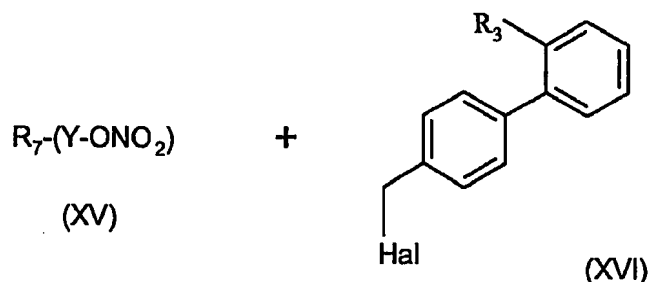
wherein Hal, Y,  $R'$  and  $R''$  are as above defined,

- 10 in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from  $-5^\circ\text{C}$  to  $60^\circ\text{C}$  or in a double phase system as already known in the literature.

- Compounds of formula (XIV) can be obtained by reacting  
15 compounds (XI) with compounds (VIIa) as above defined.

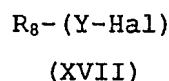
- The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as THF or  $\text{CH}_2\text{Cl}_2$  at temperatures range between  $0^\circ$ - $65^\circ\text{C}$  or in a double phase system  $\text{H}_2\text{O}/\text{Et}_2\text{O}$  at temperatures range between  $20^\circ$ - $40^\circ\text{C}$ ;  
20 and optionally acid hydrolysing the tetrazole protecting group as above described.

- E) the compounds of formula (I), as above defined, when  $s = 1$  and R is the residue of formula (II), wherein  $R_0$   
25 is the tetrazole group and  $R_1$  is selected from the groups (IIa)-(IIc) can also be obtained reacting compound of formula (XV) with a compound of formula (XVI) commercially available:

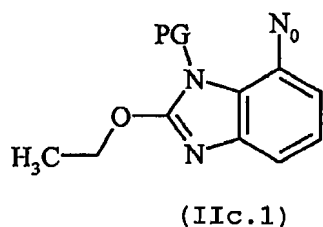
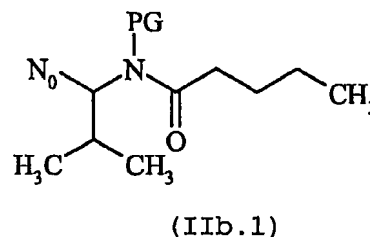
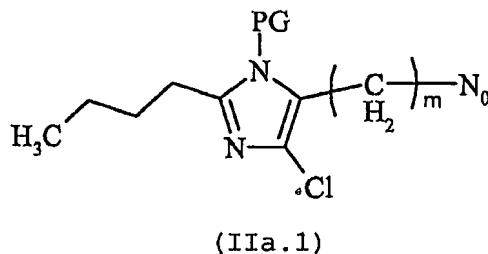


where  $\text{R}_7$  is the residue (IIa)-(IIc),  $\text{R}_3$  is the group (VA) and Hal is as already defined. The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as DMF, THF or  $\text{CH}_2\text{Cl}_2$  at temperatures range between  $-15^\circ$ - $+80^\circ\text{C}$  or in a double phase system  $\text{H}_2\text{O}/\text{Et}_2\text{O}$  at temperatures range between  $20^\circ$ - $40^\circ\text{C}$ ; and eventually acid hydrolysing the tetrazole protecting group as above described.

Compounds of formula (XV) can be obtained by reacting compounds of formula (XVII):



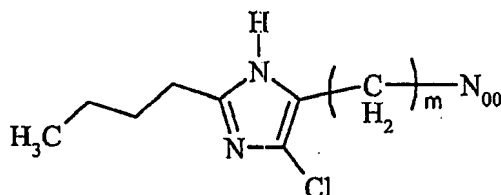
wherein  $\text{R}_8$  is the residue of formula (IIa.1), (IIb.1) or (IIc.1):



wherein PG is a N-protecting group such as BOC or trityl, with  $\text{AgNO}_3$  as already described and optionally hydrolysing the N-protective group.

Compounds (XVII) where  $R_8$  is (IIa.1) wherein  $m = 1$  and  $N_0 =$   
 5  $-\text{OCO}-$  can be obtained from the corresponding alcohols by reaction with a compound of formula (VI) or (VII) as already described.

The alcohols above defined, are obtained by known protection and reduction reactions from commercially  
 10 available compounds of formula (IIa.2):



(IIa.2)

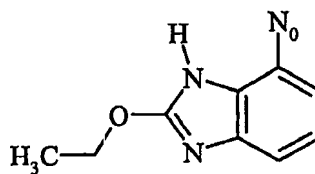
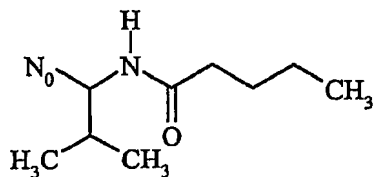
wherein  $m$  is 0 and  $N_{00}$  is  $-\text{CHO}$ .

15 Compounds (XVII) where  $R_8$  is (IIa.1) with  $m = 0$  and  $N_0 = -\text{COO}-$  or  $R_8$  is (IIb.1) or (IIc.1) with  $N_0 = -\text{COO}-$  can be obtained from the corresponding acids by reaction with compounds of formula (IX) as already described.

The corresponding acids of (IIa.1) above defined, are  
 20 obtained from compounds (IIa.2) wherein  $m$  is 0 and  $N_{00}$  is  $-\text{CHO}$  by known protection and oxidation reactions.

The corresponding acids of (IIb.1) and (IIc.1) above defined, are obtained from commercially available (IIb.2) and (IIc.2):

25



(IIb.2)

(IIc.2)

wherein N<sub>0</sub> is -COOH by known protection reactions.

The following examples are to further illustrate the  
5 invention without limiting it.

**Example 1**

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-  
10 4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)  
benzoic acid ester (corresponding to compound (4))

Triphenylmethyl chloride (4.68 g, 16.8 mmol) was added in  
portions to a solution of Losartan potassium salt (7.0 g;  
15.2 mmol) in THF (150 ml). The resulting mixture was  
15 stirred at room temperature for 24 hours. Then the  
reaction was adsorbed on silica gel and purified by flash  
chromatography (n-Hexane/AcOEt 6:4) affording 2-butyl-4-  
chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-  
biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (6.7 g,  
20 66%).

From this compound the title compound (4) can be achieved  
through two different synthetic procedure:

**Synthetic procedure A**

25 To a solution of 2-butyl-4-chloro-1-[[2'-(1-  
triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-  
1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-  
(nitrooxymethyl)benzoic acid (0.66 g, 3.38 mmol) and N,N-  
dimethylaminopyridine (0.049 g, 0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml)  
30 and THF (6 ml) cooled to 0° C, a solution of  
dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5  
ml) was slowly added and the reaction was stirred at room  
temperature for 24 hours. Then the formed dicyclohexylurea

was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (n-Hexane/AcOEt 75:25) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-  
 5 biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester (1.2 g, 55%) as a white solid.

2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-  
 10 yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester (1.2 g, 1.42 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and HCl was bubbled into the solution for 20 min. The mixture was then concentrated and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Acetone 8:2  
 15 then Acetone) affording a crude compound that was dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN and freeze-dried affording 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester as a white solid (0.304 g, 36 %).

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.73-7.56 (7H,m); 7.24 (1H,d); 7.00(4H,m); 5.60(2H,s); 5.39(2H,s); 5.28(2H,s); 2.61(2H,t); 1.53(2H,m); 1.28(2H,m); 0.82(3H,t).

#### Synthetic procedure B

25 To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-(chloromethyl)benzoic acid (0.571 g, 3.35 mmol) and N,N-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml)  
 30 and THF (6 ml) cooled to 0 °C, dicyclohexylcarbodiimide (0.644 g, 3.12 mmol) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase



was concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 75:25) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(chloromethyl)benzoic acid ester (1.56 g, yield 73%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(chloromethyl)benzoic acid ester (0.807 g, 0.98 mmol) was dissolved in CH<sub>3</sub>CN (15 ml) and AgNO<sub>3</sub> (0.305 g, 1.8 mmol) was added, in the dark and under nitrogen. The mixture was stirred at 60 °C for 6 hours. Then the precipitated silver salts were filtered off and the organic phase was diluted with ACOEt and washed with NaH<sub>2</sub>PO<sub>4</sub> (5%, 2 x 10 ml) and brine (2 x 10 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 75:25) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester (0.553 g, 66%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethylnitrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester the title compound 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester was obtained by acid hydrolysis as described in Procedure A.

### 30 Example 2

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (corresponding to compound (2))

This compound can be achieved through four different synthetic procedure:

**Synthetic procedure A**

5 To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol) (obtained in Example 1), 4-nitrooxybutanoic acid (0.536 g, 3.6 mmol) and *N,N*-dimethylaminopyridine (0.05 g, 0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20  
10 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (DCC) (0.722 g, 3.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase  
15 was concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAc 7:3) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (1.45 g, 70%).

20. 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (1.0 g, 1.25 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and HCl was bubbled into the  
25 solution for 20 min. The reaction was then concentrated and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Acetone 8:2 then Acetone) affording crude compound as a white foam. That was dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN and freeze dried to give **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (0.507 g, yield 71%) as a white solid.

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 7.66 (2H,d); 7.57 (1H,d); 7.49 (1H,d); 7.09 (2H,d); 6.95 (2H,d); 5.25 (2H,s); 4.99 (2H,s); 4.49

(2H,t); 2.54 (2H,t); 2.01 (2H,t); 1.60 (2H,m); 1.49 (2H,m);  
1.32 (4H,m); 0.84 (3H,t).

#### Synthetic procedure B

5 To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (obtained in Example 1) (1.7 g, 2.6 mmol), 4-bromobutanoic acid (0.561 g, 3.36 mmol) and N,N-dimethylaminopyridine (0.05 g, 0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml)  
10 and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated.  
15 The crude material was purified by silica gel chromatography (n-Hexane/ETOAc 75: 25) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (1.27 g, yield 60%).

20 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (1.2 g, 1.47 mmol) was dissolved in CH<sub>3</sub>CN (20 ml) and AgNO<sub>3</sub> (0.475 g, 2.8 mmol) was added in  
25 the dark and under nitrogen. The mixture was stirred at 60° C for 8 hours. Then it was partitioned between EtOAc and phosphate buffer (pH=3, 40 ml). The organic phase was washed with phosphate buffer (pH=3, 2 x 25 ml), brine, (3 x 25 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude  
30 material was purified by flash chromatography (n-Hexane/AcOEt 7:3) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

**1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester**  
(0.819 g, yield 70%) as a foam.

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester the title compound **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** was obtained by acid hydrolysis as described in Example 2, Procedure A (0.507 g, 71 %).

#### Synthetic procedure C

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (3.6 g, 8.5 mmol), *N,N*-dimethylaminopyridine (0.1 g, 0.85 mmol) and TEA (1.18 ml, 0.85 mmol) in THF (60 ml) cooled to 0 °C and under nitrogen a solution of 4-bromobutanoyl chloride (0.98 ml, 8.5 mmol) in THF (1 ml) was slowly added and the reaction was stirred at room temperature for 1.5 hours. Then it was partitioned between EtOAc and phosphate buffer (pH=3, 40 ml) and extracted with EtOAc (3 x 15 ml). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Acetone 8:2) affording **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester** (2.5 g, yield 51%) as a white solid.

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (0.56 g, 0.98 mmol) was dissolved in CH<sub>3</sub>CN (15 ml) and AgNO<sub>3</sub> (0.83 g, 4.9 mmol) was added in the dark and under nitrogen. The mixture was stirred at 60° C for 8

hours. Then it was cooled and poured into a phosphate buffer solution (pH=3, 40 ml). NaCl solid was added and the mixture was extracted with EtOAc. The organic phase was washed with phosphate buffer (pH=3, 2 x 25 ml), brine, (3 x 5 25 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/acetone 8:2 then acetone) affording crude compound as a white foam. That was dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN and freeze dried to give 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol 4-10 nitrooxybutanoic acid ester (0.3 g, yield 55%) as a white solid.

#### Synthetic procedure D

15 To a solution of 4-bromobutyric acid (0.91 g, 5.4 mmol), pentafluorophenol (1.00 g, 5.4 mmol) and DMAP (0.13 g, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) cooled to 0 °C under nitrogen, N,N-dicyclohexylcarbodiimide (1.70 g, 8.1 mmol) was added in portions. After 1 h the reaction was slowly warmed to room 20 temperature and stirred for 5 hours. The dicyclohexylurea was filtered off and the mother liquor was concentrated and purified by flash chromatography (n-Hexane/EtOAc 98:2) affording 4-bromobutyric acid pentafluorophenyl ester as a colourless oil (1.40 g, 78%).

25

A mixture of 4-bromobutyric acid pentafluorophenyl ester (0.65 g, 1.9 mmol) and AgNO<sub>3</sub> (0.83 g, 4.9 mmol) in CH<sub>3</sub>CN (8 ml) was warmed at 70 °C for 20 minutes at the microwave. The formed salts were filtered off, the solvent was 30 concentrated and the residue purified by flash chromatography (n-Hexane/EtOAc 95:5) affording 4-nitrooxybutyric acid pentafluorophenyl ester as a clear oil (0.38 g, 62 %).

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (0.48 g, 1.1 mmol), TEA (0.16 ml, 1.1 mmol) and DMAP (0.14 mg, 1.1 mmol) in DMF (3 ml), cooled to 0 °C, a solution of 4-nitrooxybutyric acid pentafluorophenyl ester (0.36 g, 1.1 mmol) in DMF (3 ml) was added. The reaction was slowly warmed to room temperature and stirred for 3 hours. Then the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 ml) and washed with a buffer solution (pH=3) then with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH 98:2) to afford the title compound (0.41 g, 66%).

15

Example 3

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester (corresponding to compound (68))

20 Using The procedure A described in Example 2 but starting from 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol) and 11-nitrooxyundecanoic acid (0.78 g, 3.36 mmol), 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester (1.65 g, 80%) was obtained.

From acid hydrolysis of this compound (1.6 g, 2.0 mmol) 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester (0.91 g, 70%) was obtained after crystallization from Et<sub>2</sub>O/n-Hexane.

(DMSO): 7.66 (2H, d); 7.57 (1H, d); 7.59 (1H, d); 7.09 (2H, d); 6.95 (2H, d); 5.25 (2H, s); 4.99 (2H, s); 4.49 (2H, t); 2.54 (2H, t); 2.01 (2H, t); 1.62 (2H, m); 1.49 (2H, m); 1.35-1.14 (16H, m); 0.84 (3H, t).

5

**Example 4**

**2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl)benzoic acid ester (corresponding to compound (5))**

10 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Prepared in Example 1) (1.0 g, 1.5 mmol), triethylamine (0.42 ml, 3.0 mmol) and *N,N*-dimethylaminopyridine (36 mg, 0.30 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml). Then 3-(chloromethyl)benzoyl chloride (0.24 ml, 1.7 mmol) was  
15 added and the reaction was stirred at room temperature for 4 hours. The mixture was diluted with EtOAC (50 ml) and the organic phase was washed with NaH<sub>2</sub>PO<sub>4</sub> (5 %, 2 x 25 ml), NaHCO<sub>3</sub> (5 %, 2 x 25 ml), brine (2 x 25 ml), dried over  
20 Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAC 75:25) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(chloromethyl)benzoic acid ester (1.0 g, 81 %) as an oil.

25

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-

(chloromethyl)benzoic acid ester (0.66 g, 0.20 mmol) was suspended in CH<sub>3</sub>CN (10 ml) and NaI (0.24 g, 1.6 mmol) was added. The reaction was refluxed for 1 hour, then diluted with EtOAc (25 ml). The organic phase was washed with H<sub>2</sub>O (3 x 25 ml), dried over NaSO<sub>4</sub> and concentrated. The crude material was dissolved in CH<sub>3</sub>CN (4 ml) and AgNO<sub>3</sub> (0.34 g, 2 mmol) was added in the dark and under nitrogen. The reaction was stirred at room temperature for 2 hours, then it was diluted with EtOAc (10 ml). The organic phase was washed with NaH<sub>2</sub>PO<sub>4</sub> (5 %, 2 x 10 ml) and brine (2 x 10 ml), dried over NaSO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (Hexane/EtOAc 75:25), affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl)benzoic acid ester (230 mg, 33 %).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl)benzoic acid ester (0.23 g, 0.27 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and HCl was bubbled in the solution. 10 minutes later the reaction was concentrated and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/acetone 8:2 and then acetone). The yellow foam obtained was treated over decolorizing carbon, dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN and



freeze-dried affording 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol m-nitrobenzylbenzoic acid ester as a white solid (0.11 g, 63 %).

5 (CDCl<sub>3</sub>): 7.90 (2H,m); 7.78 (1H,d); 7.56 (3H,m); 7.40 (1H,m); 7.19 (1H,d); 7.06 (2H,d); 6.83 (2H,d); 5.40 (2H,s); 5.24 (2H,s); 5.14 (2H,s); 2.47 (2H,t); 1.61 (2H,m); 1.32 (2H,m); 0.87 (3H,m).

#### 10 Example 5

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester (corresponding to compound (69))

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol  
 15 (prepared in Example 1) (2.0 g, 3.0 mmol), 6-bromohexanoic acid (0.90 g, 4.6 mmol), *N,N*-dimethylaminopyridine (38 mg, 0.3 mmol), triethylamine (1.3 ml, 9.3 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and the solution was cooled to 0°C. Then  
 20 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) (0.94 g, 9.3 mmol) was added and the reaction was slowly warmed to room temperature and stirred overnight. The organic phase was washed with NaH<sub>2</sub>PO<sub>4</sub> (5 %, 20 ml) and brine (20 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and purified by flash  
 25 chromatography (n-Hexane/EtOAc 7:3) affording 2-butyl-4-

chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-  
biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-  
bromohexanoic acid ester as an oil (1.94 g, 76 %).

5 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-  
yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-  
bromohexanoic acid ester (0.77 g, 0.90 mmol) and NaI (0.30  
g, 2.0 mmol) were dissolved in CH<sub>3</sub>CN (10 ml) and the  
mixture was refluxed for 1 hour. Then it was diluted with  
10 EtOAc (50 ml) and the organic phase was washed with H<sub>2</sub>O (2  
x 25 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude was  
suspended in CH<sub>3</sub>CN (7 ml) and AgNO<sub>3</sub> (0.60 g, 3.5 mmol) was  
added. The reaction was stirred at room temperature, in the  
dark and under nitrogen, for 3 hours. Then it was  
15 partitioned between EtOAc (30 ml) and phosphate buffer  
(pH=3, 25 ml). The organic phase was washed with phosphate  
buffer (pH=3, 2 x 25 ml) and brine (3 x 25 ml), dried over  
Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by  
flash chromatography (n-Hexane/EtOAc 7:3) affording 2-  
20 butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-  
yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-  
nitrooxyhexanoic acid ester as a foam (0.69 g, 64 %).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-  
25 yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-  
nitrooxyhexanoic acid ester (0.88 g) was dissolved in

CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and HCl was bubbled into the solution for 20 minutes. The mixture was then concentrated and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/acetone 8:2 and then acetone) affording the product as a yellow foam. That was treated  
5 with decolorizing carbon, dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN and freeze-dried to give product **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester** as a white solid (0.41 g, 68 %).

10 (CDCl<sub>3</sub>): 7.79 (1H, d); 7.63-7.49 (2H, m); 7.41 (1H, d); 7.08 (2H, d); 6.77 (2H, d); 5.14 (2H, s); 4.88 (2H, s); 4.38 (2H, t); 2.38 (2H, t); 2.06 (2H, m); 1.70-1.50 (6H, m); 1.37-1.30 (4H, m); 0.85 (3H, t).

15 **Example 6**

**2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid (3-nitrooxy)propyl ester (corresponding to compound (7))**

To a solution of 2-butyl-4-chloro-5-formyl imidazole (1.2 g, 6.4 mmol) in t-ButOH (35 ml) and 5% aqueous Na<sub>2</sub>HPO<sub>4</sub>  
20 solution (25 ml), a solution of KMnO<sub>4</sub> (6.1 g, 38.6 mmol) in water (40 ml) was added. After 6 minutes at room temperature, the mixture was quenched by addition of 40% aqueous NaHSO<sub>3</sub> solution. The suspension was filtered,  
25 washed with H<sub>2</sub>O and the filtrate was freeze-dried. The residue was taken up with H<sub>2</sub>O (50 ml) acidified to pH 2.5 with HCl 3N and extracted with EtOAc (3 x 70 ml). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and

evaporated to dryness to give **2-butyl-4-chloro-imidazole 5-carboxylic acid** (1.07 g, 83%) as a white solid.

To a solution of 2-butyl-4-chloro-imidazole 5-carboxylic acid (0.61 g, 3 mmol), 3-bromopropanol (0.52 g, 3.74 mmol) and *N,N*-dimethylaminopyridine (0.08 g, 0.65 mmol) in THF (12 ml) cooled to 0° C, dicyclohexylcarbodiimide (0.91 g, 4.4 mmol) was slowly added in portions and the reaction was stirred at room temperature for 4 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (*n*-Hexane/AcOEt 8:2) affording **2-butyl-4-chloro-imidazole 5-carboxylic acid 3-bromopropyl ester** (0.5 g, 50%) as a white foam.

2-butyl-4-chloro-imidazole 5-carboxylic acid 3-bromopropyl ester (0.807 g, 2.47 mmol) was dissolved in CH<sub>3</sub>CN (15 ml) and AgNO<sub>3</sub> (0.63 g, 3.7 mmol) was added. The mixture was stirred at room temperature for 8 h. Then the precipitated silver salts were filtered off and the organic phase was diluted with AcOEt and washed with NaH<sub>2</sub>PO<sub>4</sub> (5%, 2 x 10 ml) and brine (2 x 10 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (*n*-Hexane/AcOEt 70:30) affording **2-butyl-4-chloro-imidazole 5-carboxylic acid 3-nitrooxypropyl ester** (0.377 g, 50%).

To a solution of 2-butyl-4-chloro-imidazole 5-carboxylic acid 3-nitrooxypropyl ester (0.76 g, 2.5 mmol) in dimethylacetamide (DMA) (13 ml) cooled to 0 °C and under nitrogen, potassium *tert*-butylate (0.28 g, 2.5 mmol) was slowly added in portions. After 10 min stirring a solution of *N*-(triphenylmethyl)-5-(4'-bromomethylbiphenyl-2-yl)-tetrazole (1.7 g, 3 mmol) in DMA (10 ml) was added and the

mixture was stirred at room temperature for 1 h. Then the mixture was partitioned between water and EtOAc. The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAc 7:3) affording 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid 3-nitrooxypropyl ester (1.56 g, 80%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid 3-nitrooxypropyl ester (1 g, 1.28 mmol) the title compound (white solid) was achieved through acid hydrolysis as described for analogous compound in **Example 1** procedure A (0.28 g, 40%).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.60-7.20 (4H,m); 7.12 (2H,d); 6.92 (2H,d); 5.72 (2H,s); 4.58 (2H,t); 4.50 (2H,t); 2.54 (2H,t); 2.31 (2H,m); 1.49 (2H,m); 1.32 (2H,m); 0.84 (3H,t).

#### Studies on vascular tone

The ability of the nitroderivatives of ARB to induce vasorelaxation in comparison to native ARB, was tested *in vitro* in isolated rabbit thoracic aorta preparations (Wanstall J.C. et al., Br. J. Pharmacol., 134:463-472, 2001). Male New Zealand rabbits were anaesthetized with thiopental-Na (50 mg/kg, iv), sacrificed by exsanguinations and then the thorax was opened and the aorta dissected. Aortic ring preparations (4 mm in length) were set up in physiological salt solution (PSS) at 37°C in small organ chambers (5 ml). The composition of PSS was (mM): NaCl 130, NaHCO<sub>3</sub> 14.9, KH<sub>2</sub>PO<sub>4</sub> 1.2, MgSO<sub>4</sub> 1.2, HEPES 10, CaCl<sub>2</sub>, ascorbic acid 170 and glucose 1.1 (95% O<sub>2</sub> /5% CO<sub>2</sub> ; pH 7.4). Each ring was mounted under 2 g passive tension. Isometric tension was recorded with a Grass transducer (Grass FT03)

attached to a BIOPAC MP150 System. Preparations were allowed to equilibrate for 1h, and then contracted submaximally with noradrenaline (NA, 1  $\mu$ M) and, when the contraction was stable, acetylcholine (ACh, 10  $\mu$ M) was added. A relaxant response to ACh indicated the presence of a functional endothelium. Vessels that were unable to contract NA or showed no relaxation to ACh were discarded. When a stable precontraction was reached, a cumulative concentration-response curve to either of the vasorelaxant agents was obtained in the presence of a functional endothelium. Each arterial ring was exposed to only one combination of inhibitor and vasorelaxant. Moreover, the effect of the soluble guanylyl cyclase inhibitor ODQ (1-H-(1,2,4)-oxadiazol(4,3-a)quinoxalin-1-one) on vasorelaxation elicited by the compounds was examined preincubating the aortic rings with ODQ (10  $\mu$ M) for 20 min. Responses to relaxing agents are expressed as a percentage of residual contraction and plotted against concentration of test compound.  $IC_{50}$  values (where  $IC_{50}$  is the concentration producing 50% of the maximum relaxation to the test compound) were interpolated from these plots. During the experimental period, the plateau obtained with NA was stable without significant spontaneous loss of contraction in the aortic rings. Under these experimental conditions, the ARB losartan, did not produce relaxation at any of the concentration tested, the curve being not different from that built up in the presence of vehicle alone. As shown in Table 1, the nitroderivatives of the invention were able to induce relaxation in a concentration-dependent manner. Furthermore, in experiments performed in the presence of ODQ (10  $\mu$ M), the vasorelaxant responses to tested compounds were inhibited.

Table 1

Compound	IC <sub>50</sub> (μM) ± sem
Losartan	no effect up to 100 μM
Compound of EX.1	33 ± 12
Compound of EX.2	15 ± 3
Compound of EX.4	54 ± 16
Compound of EX.5	18 ± 6

IC<sub>50</sub> is the concentration which inhibits 50% of the response.

5 **Effect of losartan nitroderivative on inflammatory pathways *in vitro***

The experiments were performed using RAW 264.7 monocyte macrophage cell line. Cells were stimulated in the presence of lipopolysaccharide (LPS) (1 μg/ml) for 16 hrs. At the  
10 end of the incubation, the culture media were collected and analyzed for nitrite content using a standard Griess reaction.

The results reported in Table 2 are expressed as % of nitrite content for each treatment vs. LPS-treated samples.

15

Table 2

Study of inhibition of LPS-induced nitrite accumulation in RAW 264.7 macrophages		
Compound	Concentration (μM)	Nitrite (% vs vehicle)
Losartan	25	99 ± 9
Compound of EX.4	25	61 ± 3

As shown in Table 2, differently from the parent compound, the nitroderivative (compound of Ex.4) was able to inhibit the accumulation of nitrites induced by LPS.

**5 Study of antiplatelet activity of losartan nitroderivatives in vitro**

The ability of losartan nitroderivatives to inhibit platelet aggregation was evaluated *in vitro* in human platelets. Platelet aggregation was measured in 0.25 ml platelet rich plasma (PRP) samples according to Born method (Gresele P, Arnout J, Deckmyn H, et al., J Clin Invest. 1987;80:1435-45). Aggregating agent used was U46619, a TxA<sub>2</sub> analog, based on the evidence that this agonist is sensitive to the effects of nitric oxide. Compounds were incubated at 37°C for 2 min before adding the aggregating agent. Aggregation was followed for 5 min and the maximal amplitude (cm) was measured. DMSO (0.05% final concentration) was used as vehicle. Compounds were tested at concentrations ranging from 10 to 100µM.

20

**Table 3**

Study of antiplatelet activity of losartan nitroderivatives vs losartan in human platelets	
Compound	Platelet aggregation (PRP) (incubation time: 2 min) IC <sub>50</sub> µM
Losartan	33
Compound of EX.1	5
Compound of EX.2	11



As shown in Table 3, the nitroderivatives were able to significantly inhibit platelet aggregation induced by U46619. Losartan showed a weak effect.

5 **Study of antihypertensive activity of losartan nitroderivative in vivo**

The ability of losartan nitroderivative (compound of Ex.2) to decrease blood pressure was evaluated in conscious spontaneously hypertensive rats (SHRs). Two groups of SHRs  
10 (250-300 g) received a daily oral dose of either losartan (10 mg/kg po) or losartan nitroderivative (equimolar dose) for 3 days. Systolic blood pressure (SBP) and heart rate were monitored by telemetry at different time points after dosing.

15

**Table 4**

Systolic blood pressure (mmHg)				
Compound	Baseline	30 min	12 hrs	24 hrs
Losartan (10 mg/kg po)	143	133	135	136
Compound of EX.2 (12 mg/kg po)	143	115	126	128

As shown in Table 4, differently from the parent compound, the nitroderivative (compound of Ex.2) was able to induce a clear reduction in blood pressure levels over the treatment  
20 period.

## CLAIMS

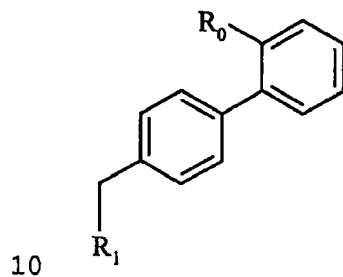
1. A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof:



wherein:

s is an integer equal to 1 or 2;

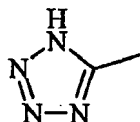
R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



(II)

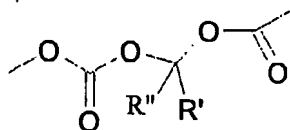
wherein:

R<sub>0</sub> is



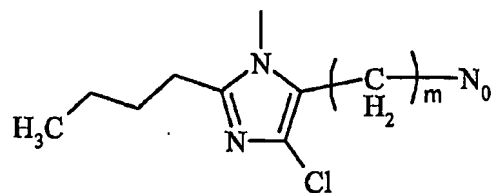
15 or -N<sub>0</sub> which is a group capable to bind to Y, having one of the following meaning:

-COO-, -O-, -CONH-, -OCO-, -OCOO- or

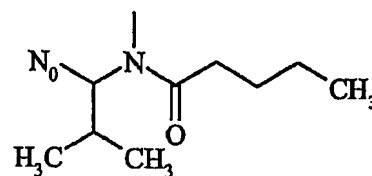


20 wherein R' and R'' are the same or different, and are H or straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

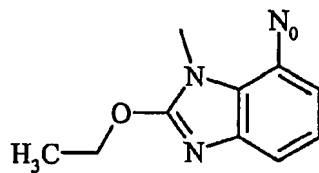
R<sub>1</sub> is selected from the group consisting of:



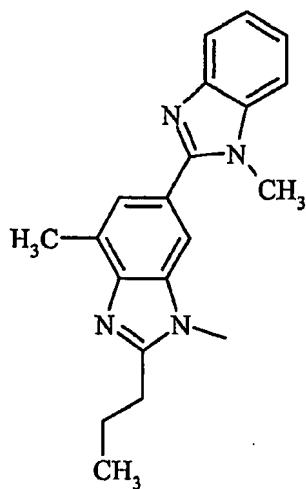
(IIa)



(IIb)

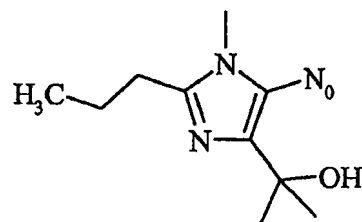


(IIc)



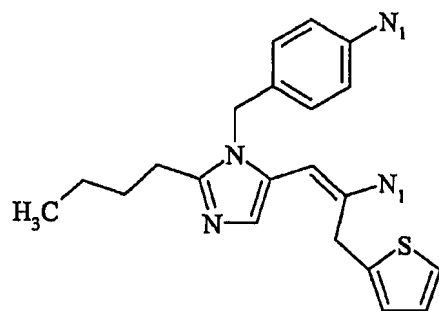
(IIId)

or



(IIe)

wherein  $m$  is an integer equal to 0 or 1 and  $N_0$  is as above defined;



(III)

wherein  $N_1$  has the same meaning as  $N_0$  or is equal to  $-\text{COOH}$ ; with the proviso that at least one of the groups  $N_1$  is equal to  $-\text{COO}-$  or  $-\text{CONH}-$ , i.e. it is a group capable to bind to Y;

5 Y is a bivalent radical having the following meaning:

a)

- straight or branched  $\text{C}_1\text{-C}_{20}$  alkylene, preferably  $\text{C}_1\text{-C}_{10}$ , being optionally substituted with one or more of the substituents selected from the group consisting of: halogen

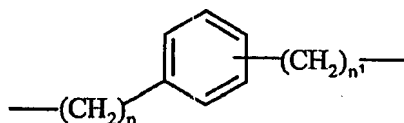
10 atoms, hydroxy,  $-\text{ONO}_2$  or  $\text{T}_0$ , wherein  $\text{T}_0$  is

$-\text{OC}(\text{O})(\text{C}_1\text{-C}_{10} \text{ alkyl})-\text{ONO}_2$  or  $-\text{O}(\text{C}_1\text{-C}_{10} \text{ alkyl})-\text{ONO}_2$ ;

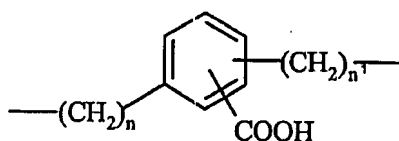
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from

15 1 to 10 carbon atoms, preferably  $\text{CH}_3$ ;

b)

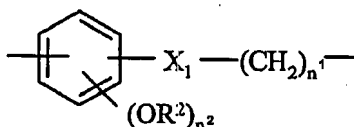


c)



20 wherein  $n$  is an integer from 0 to 20, and  $n^1$  is an integer from 1 to 20;

d)

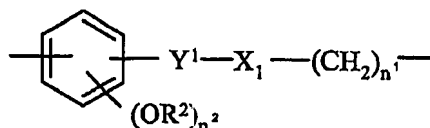


wherein:

25  $n^1$  is as defined above and  $n^2$  is an integer from 0 to 2;

$\text{X}_1 = -\text{OCO}-$  or  $-\text{COO}-$  and  $\text{R}^2$  is H or  $\text{CH}_3$ ;

e)

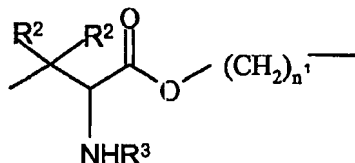


wherein:

n<sup>1</sup>, n<sup>2</sup>, R<sup>2</sup> and X<sub>1</sub> are as defined above;

Y<sup>1</sup> is -CH<sub>2</sub>-CH<sub>2</sub>- or -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2</sup></sub>-;

5 f)



wherein:

n<sup>1</sup> and R<sup>2</sup> are as defined above, R<sup>3</sup> is H or -COCH<sub>3</sub>;

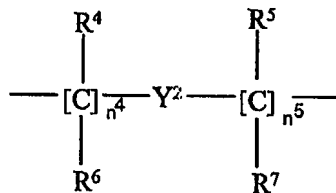
with the proviso that when Y is selected from the bivalent  
10 radicals mentioned under b)-f), the -ONO<sub>2</sub> group is linked  
to a -(CH<sub>2</sub>)<sub>n<sup>1</sup></sub> group;

g)



wherein X<sub>2</sub> is -O- or -S-, n<sup>3</sup> is an integer from 1 to 6,  
15 preferably from 1 to 4, R<sup>2</sup> is as defined above;

h)



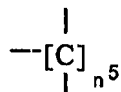
wherein:

n<sup>4</sup> is an integer from 0 to 10;

20 n<sup>5</sup> is an integer from 1 to 10;

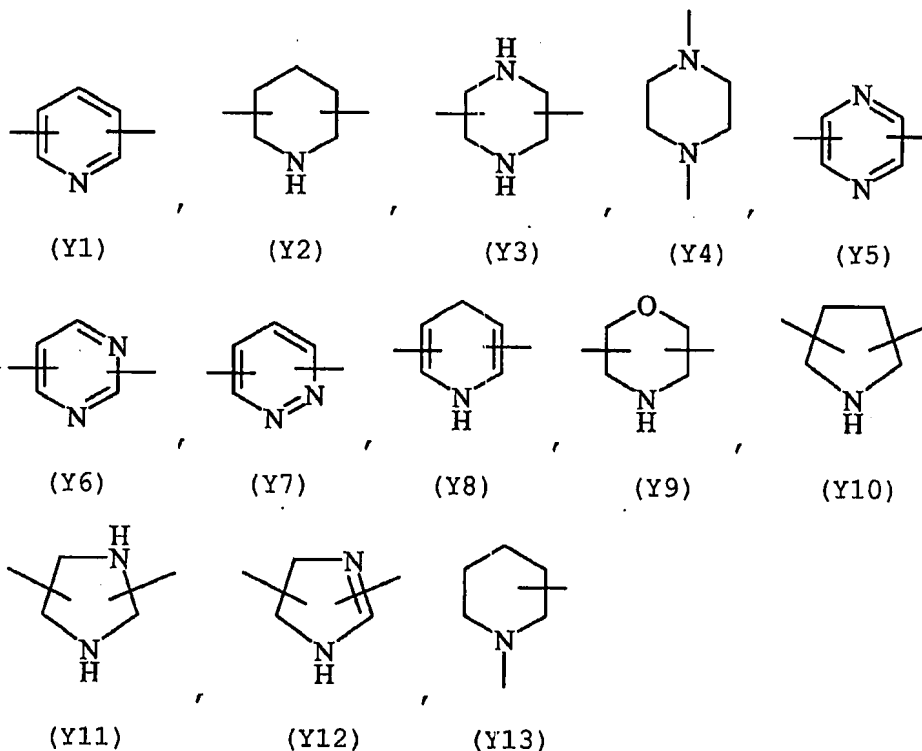
R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> are the same or different, and are H or  
straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>  
are H;

wherein the  $-\text{ONO}_2$  group is linked to



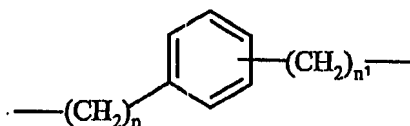
wherein  $n^5$  is as defined above;

$\text{Y}^2$  is an heterocyclic saturated, unsaturated or aromatic 5  
 5 or 6 members ring, containing one or more heteroatoms  
 selected from nitrogen, oxygen, sulfur,  
 and is selected from



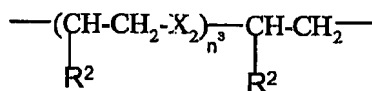
15 2. A compound of general formula (I) or a pharmaceutically  
 acceptable salt or stereoisomer thereof according to claim  
 1 wherein Y is a bivalent radical having the following  
 meaning:

- a) straight or branched  $\text{C}_1\text{-C}_{10}$  alkylene, being optionally  
 20 substituted with  $\text{T}_0$ , wherein  $\text{T}_0$  is as above defined;  
 b)



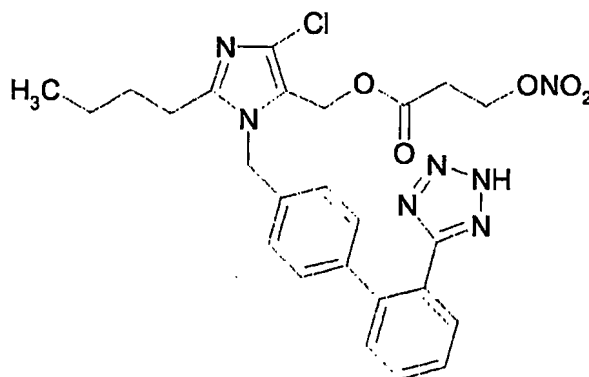
wherein n is an integer equal to 0 or 1, and n<sup>1</sup> is an integer equal to 1; with the proviso the -ONO<sub>2</sub> group is linked to a -(CH<sub>2</sub>)<sub>n<sup>1</sup></sub> group;

5 g)

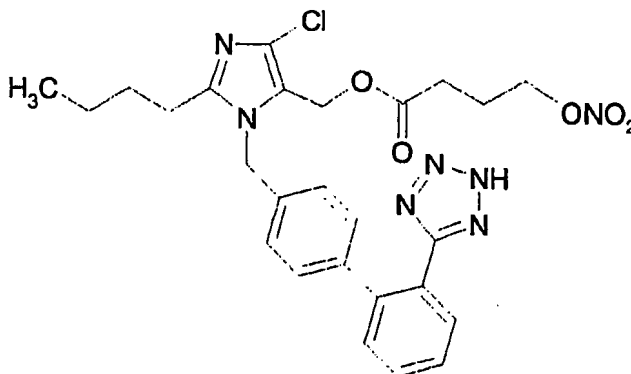


wherein  $X_2$  is -O- or -S-,  $n^3$  is an integer equal to 1 and  $R^2$  is H.

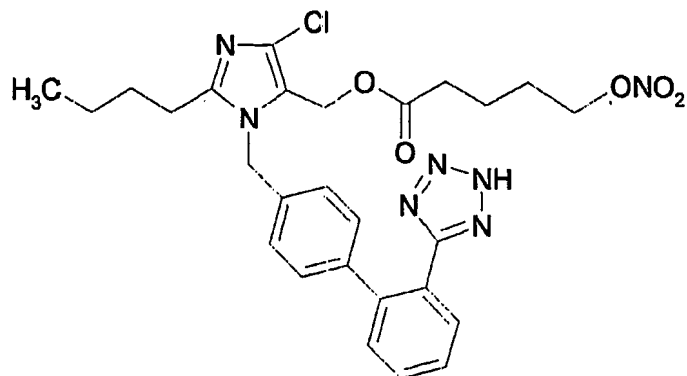
10 3. A compound according to claims 1-2, selected from the  
group consisting of:



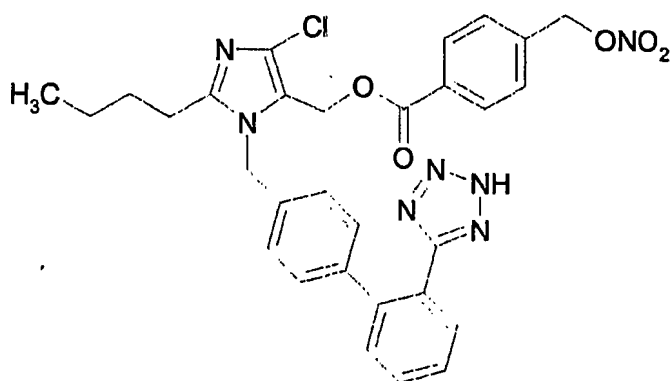
(1)



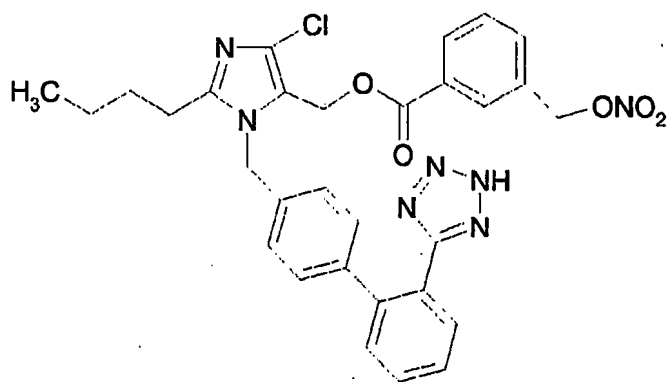
(2)



(3)

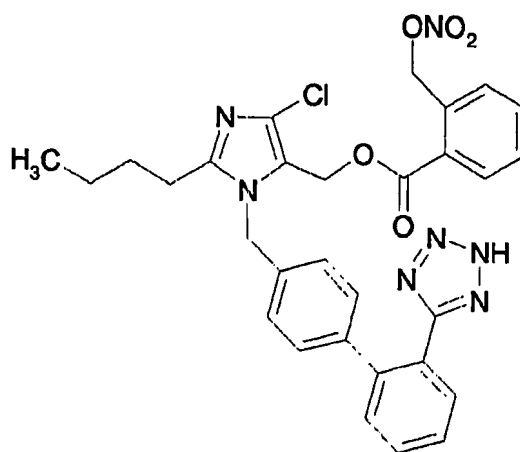


(4)

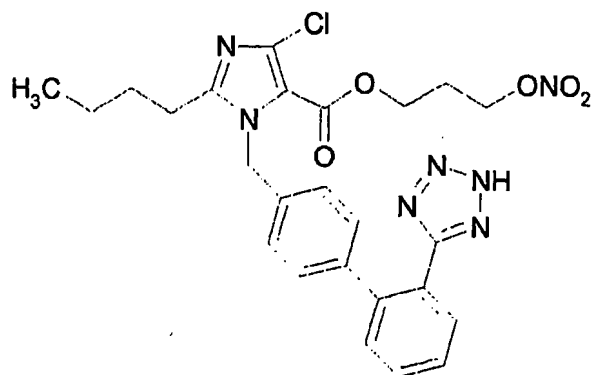


(5)

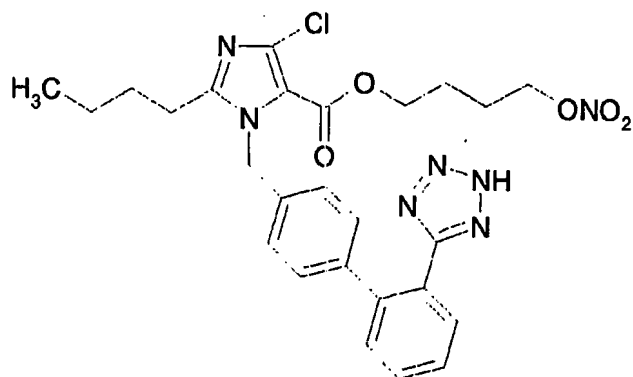




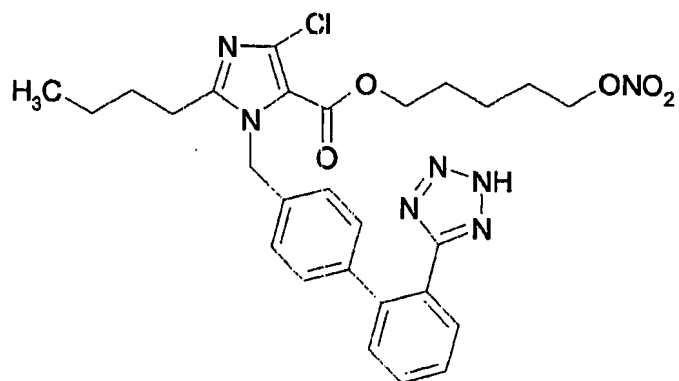
(6)



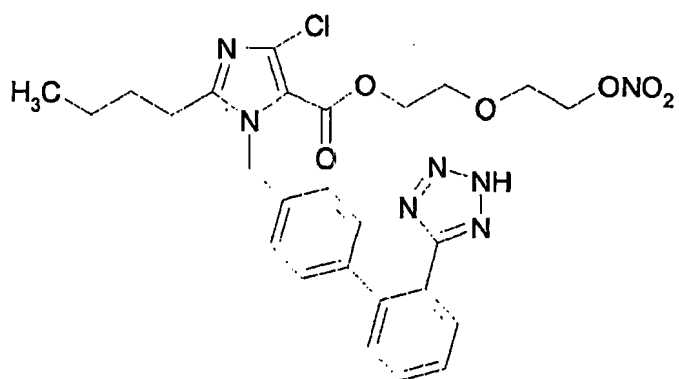
(7)



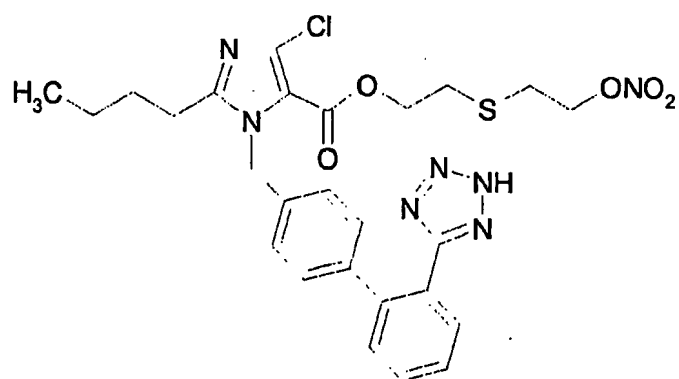
(8)



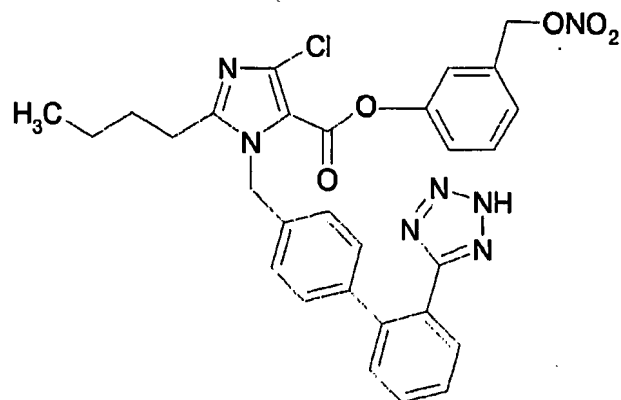
(9)



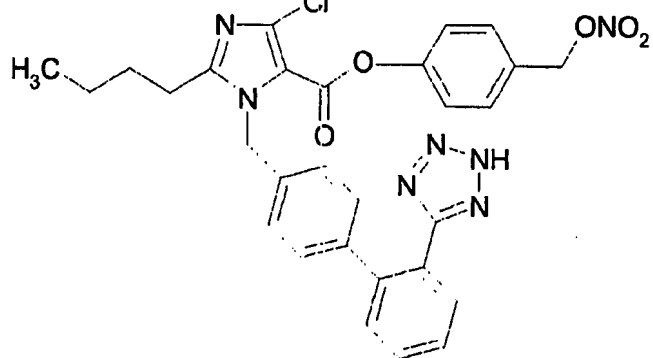
(10)



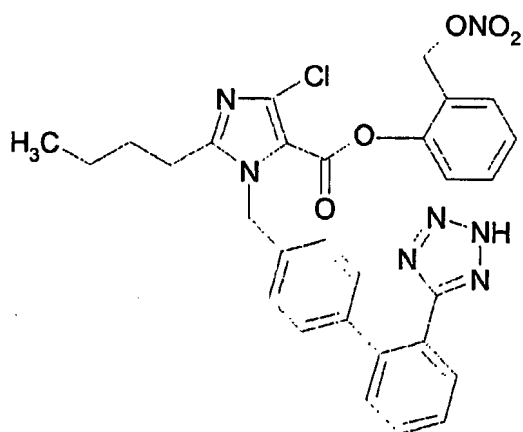
(11)



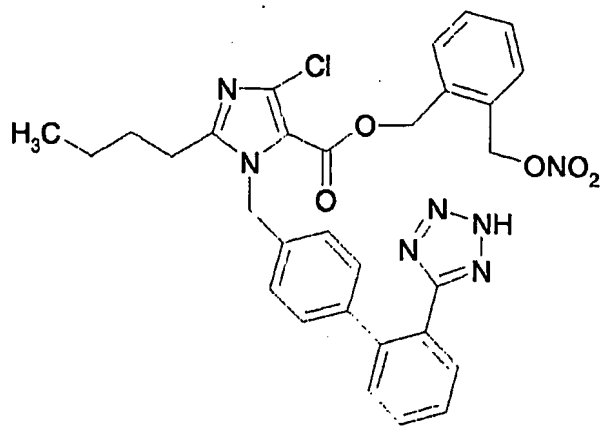
(12)



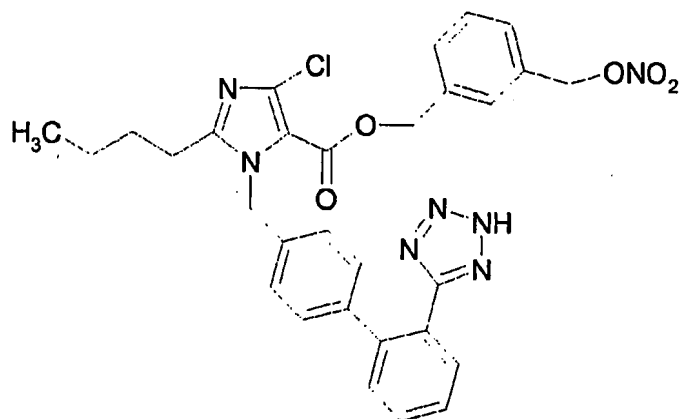
(13)



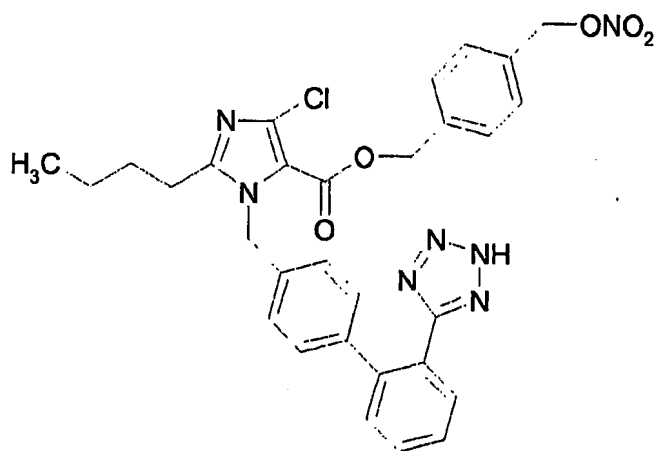
(14)



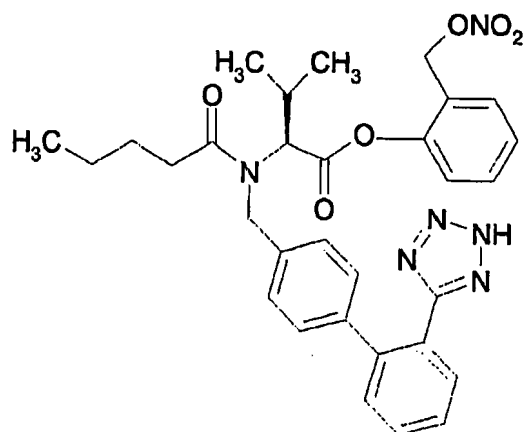
(15)



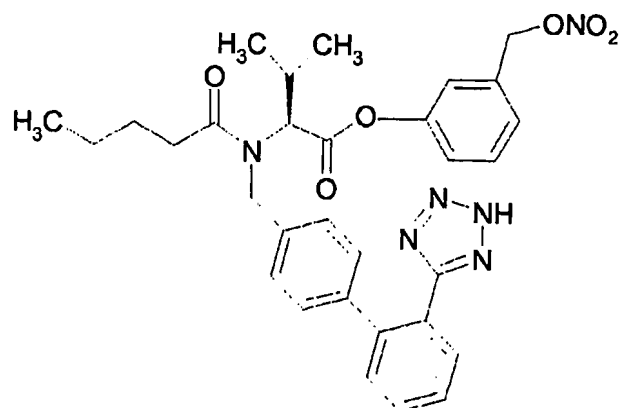
(16)



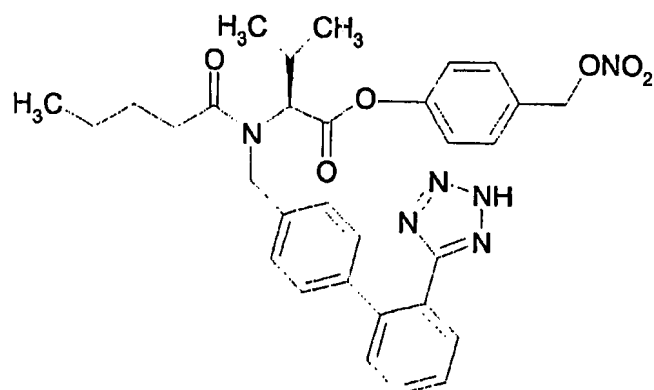
(17)



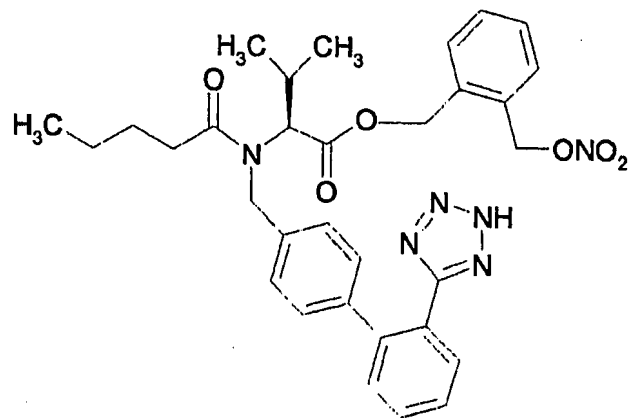
(18)



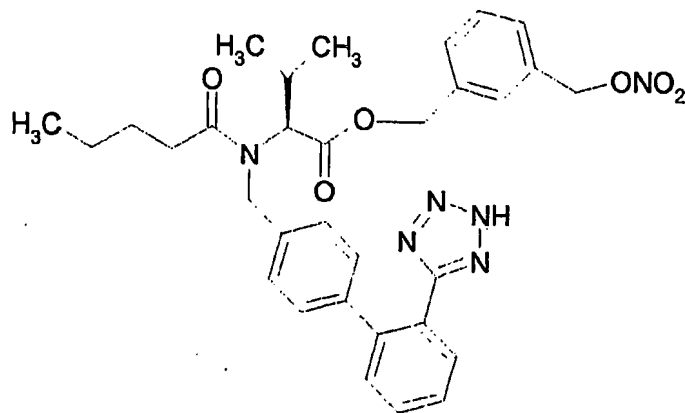
(19)



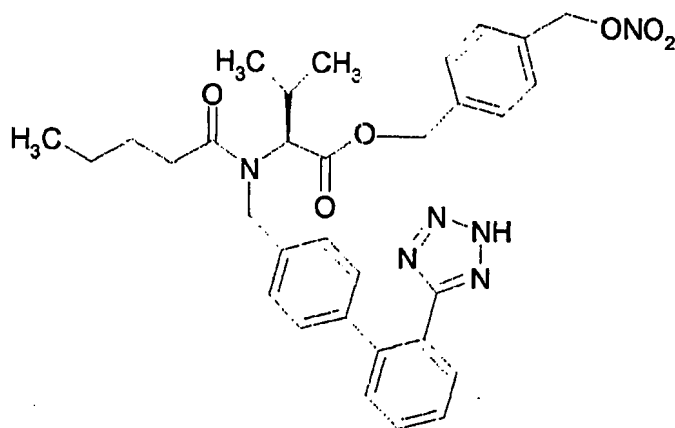
(20)



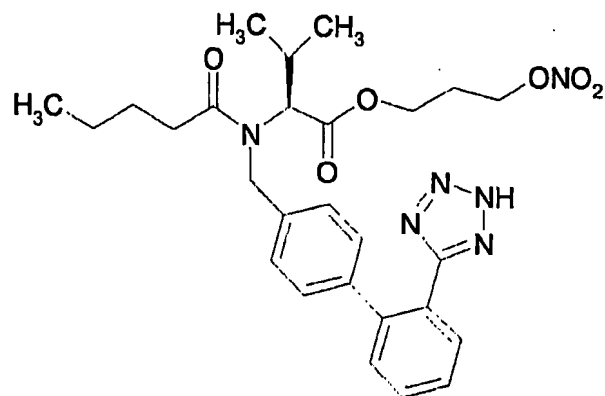
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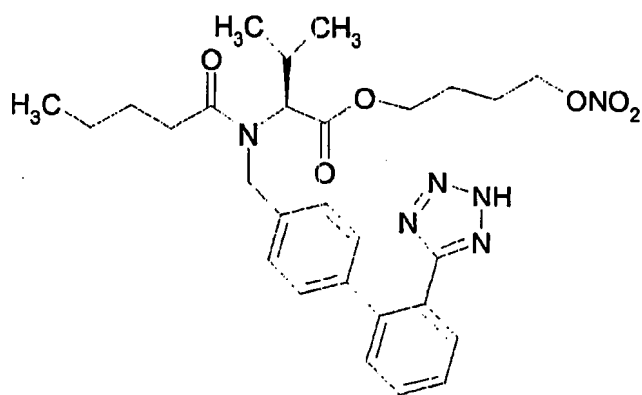
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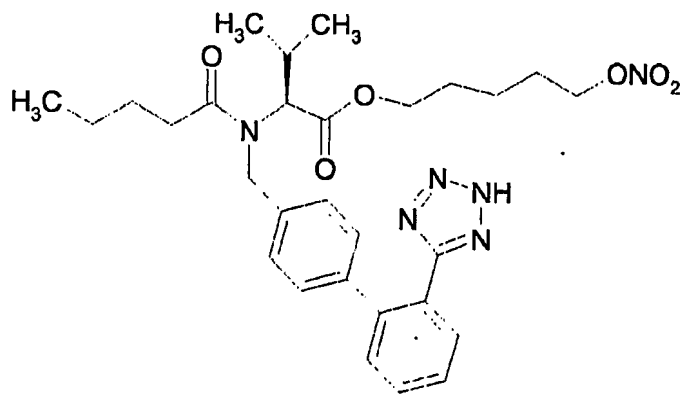
(23)



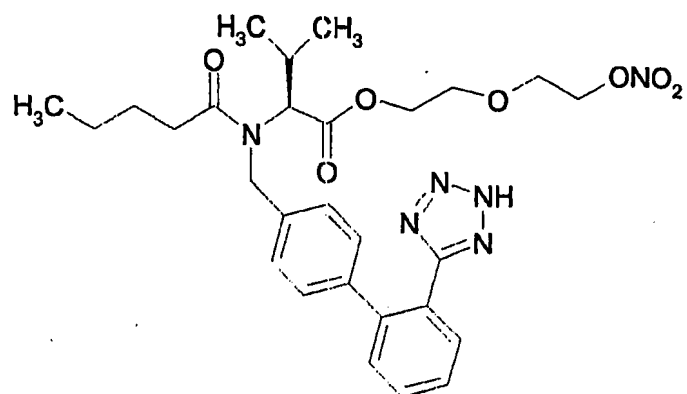
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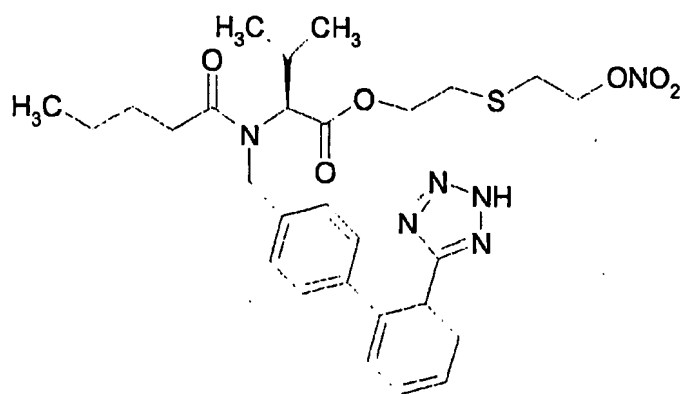
(25)



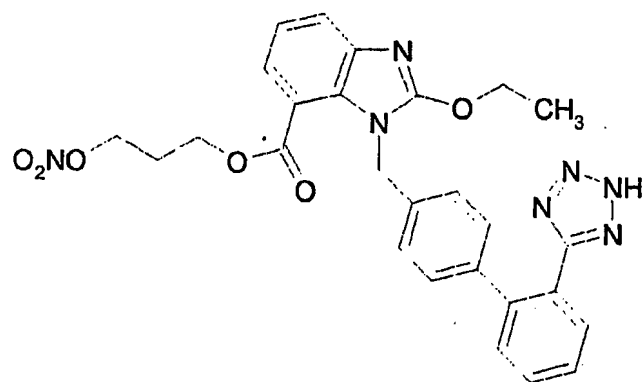
(26)



(27)

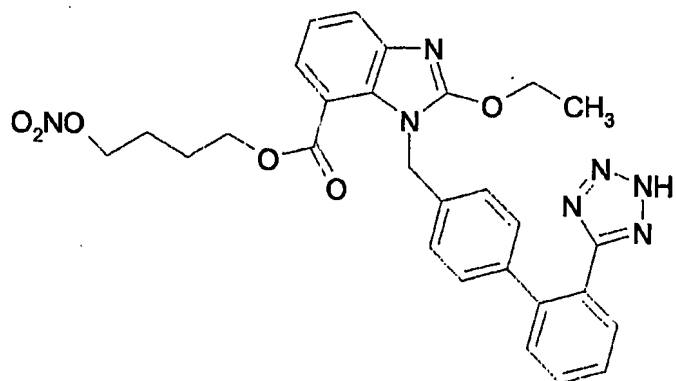


(28)

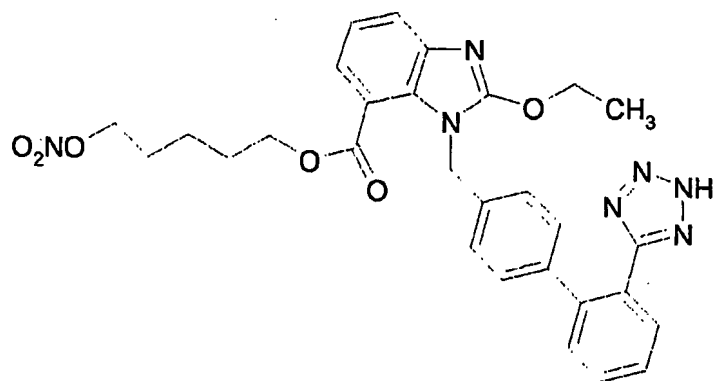


(29)

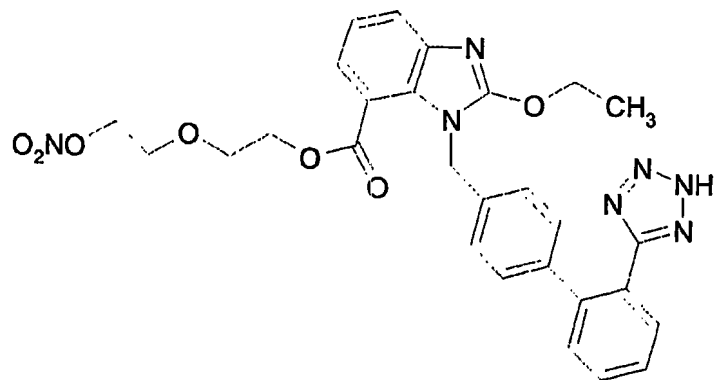




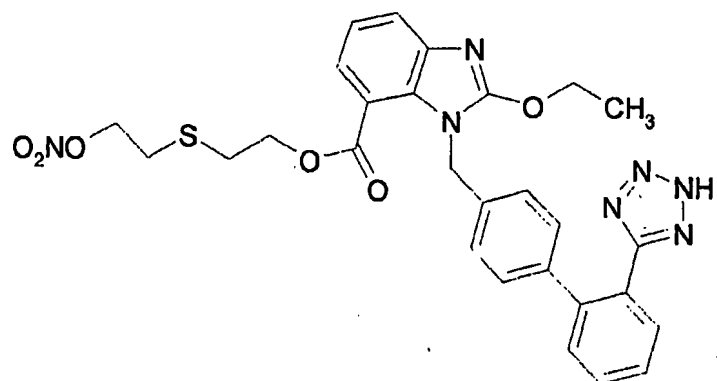
(30)



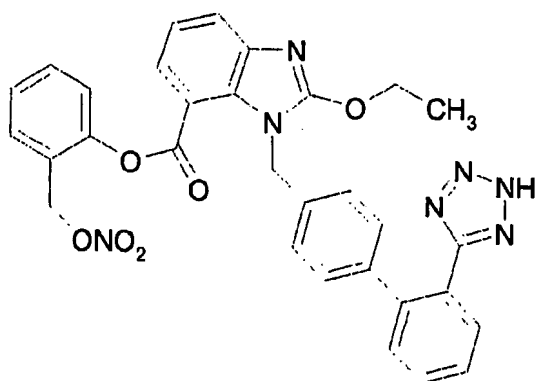
(31)



(32)

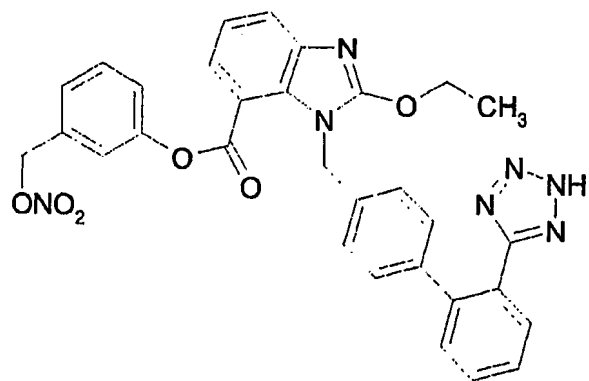


(33)

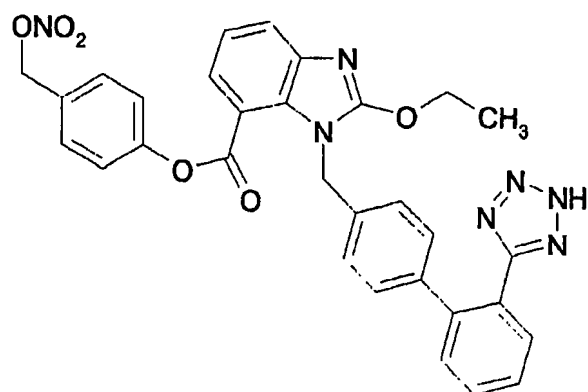


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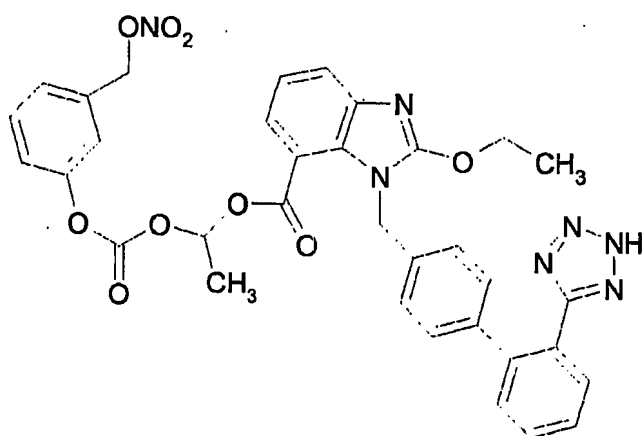
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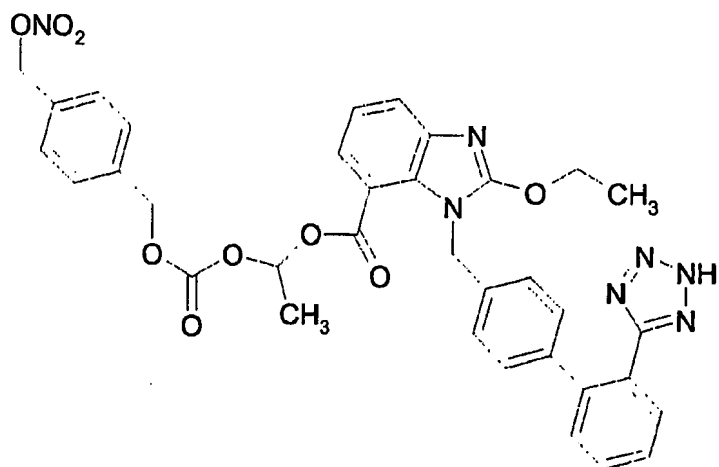
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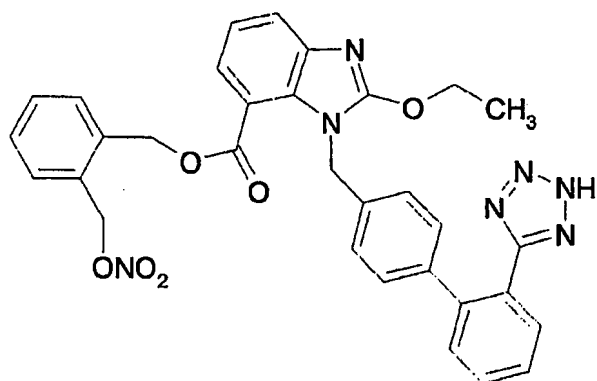
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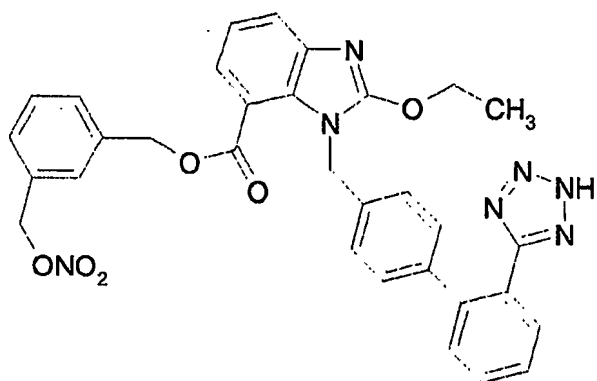
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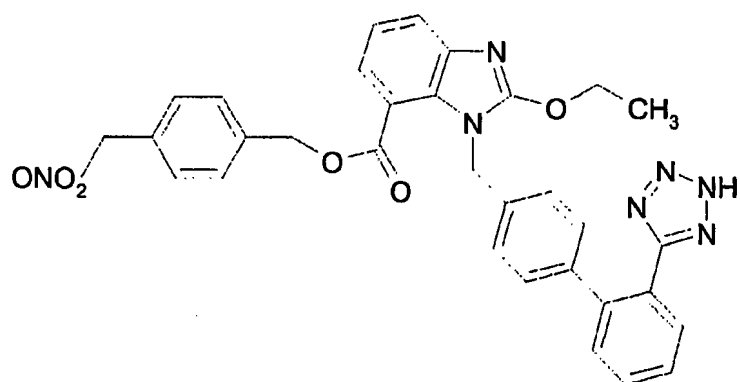
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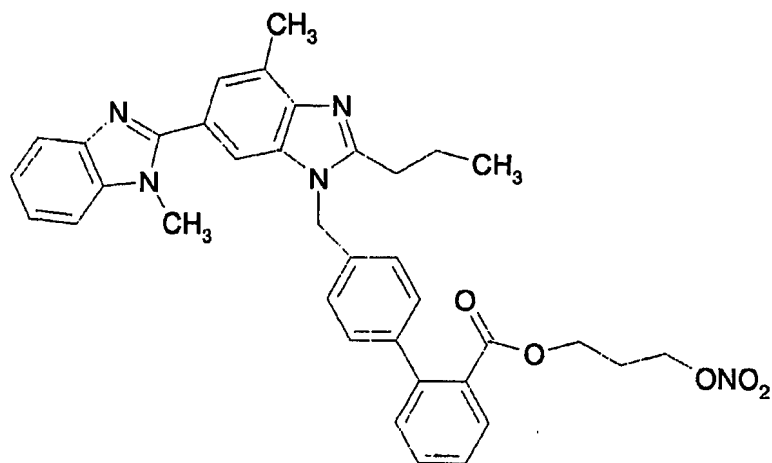
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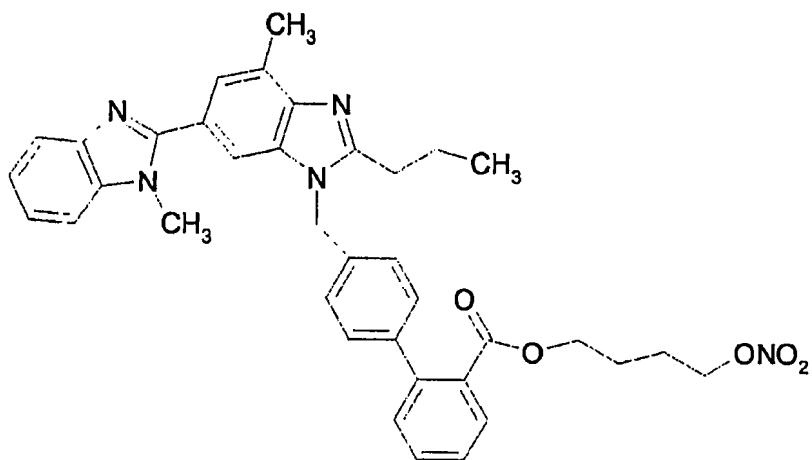
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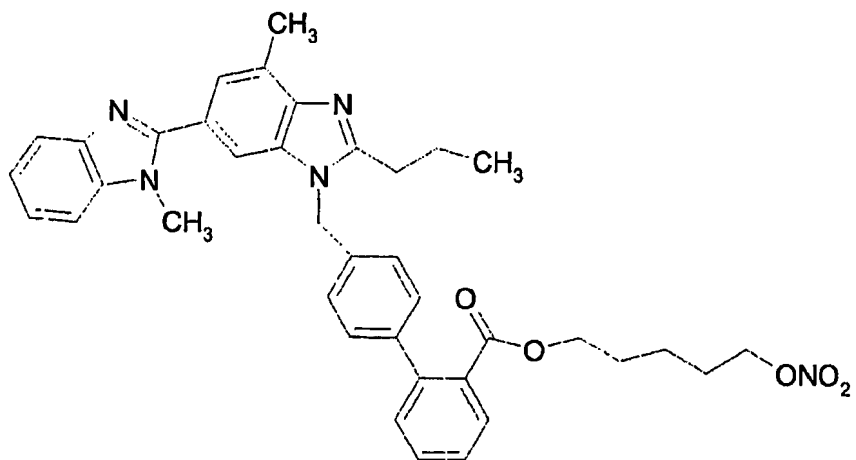
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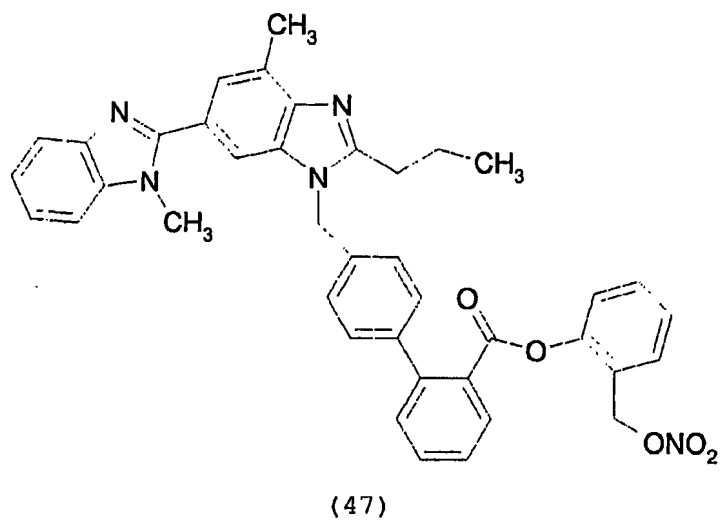
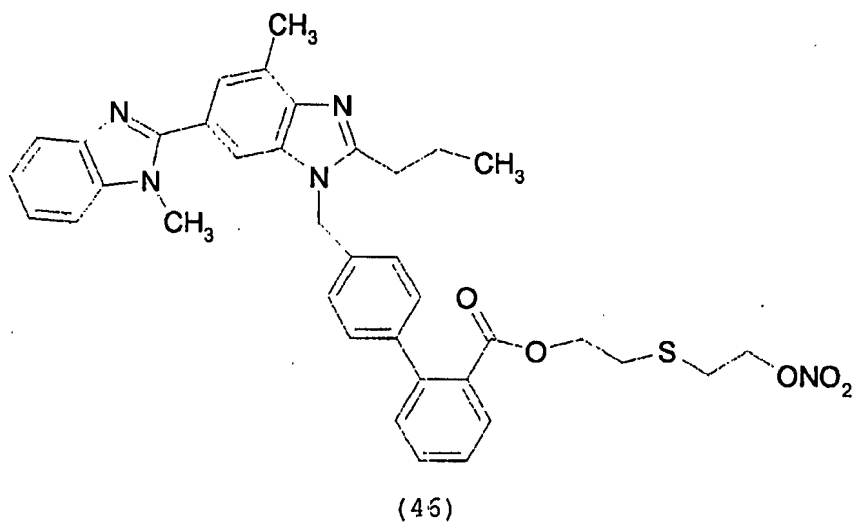
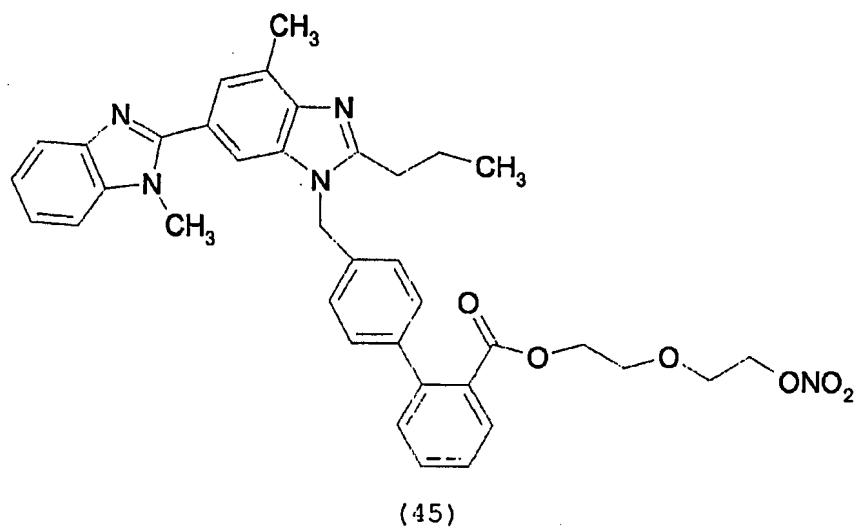
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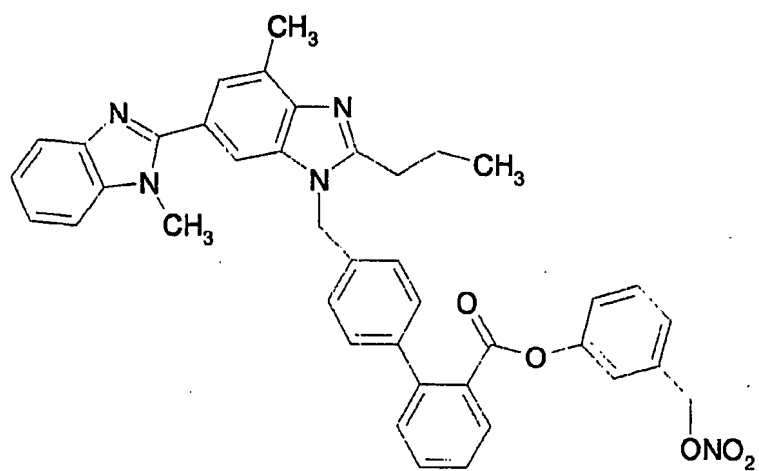


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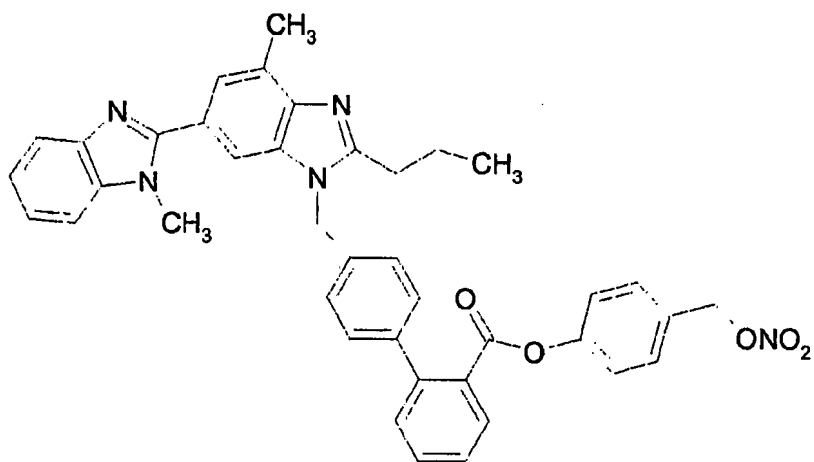


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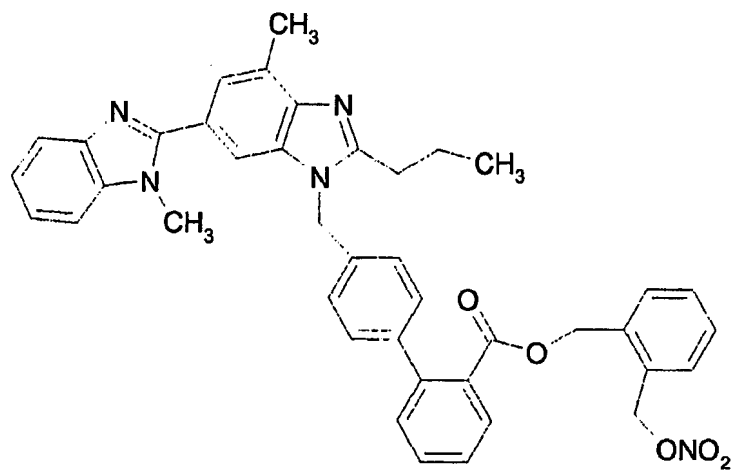




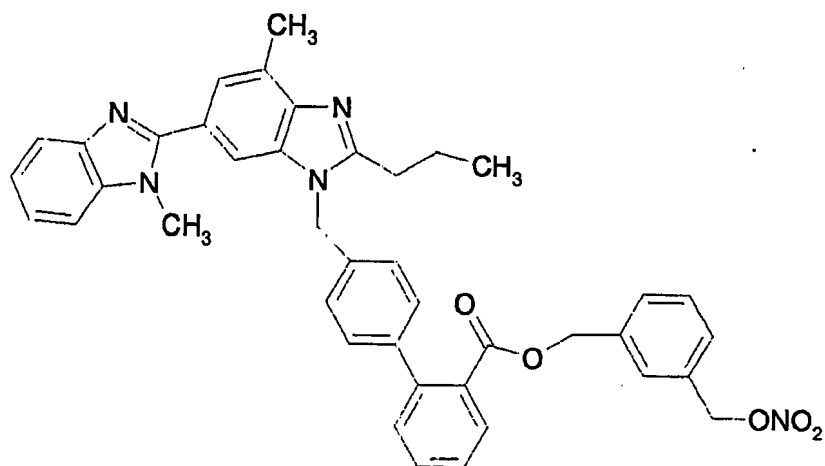
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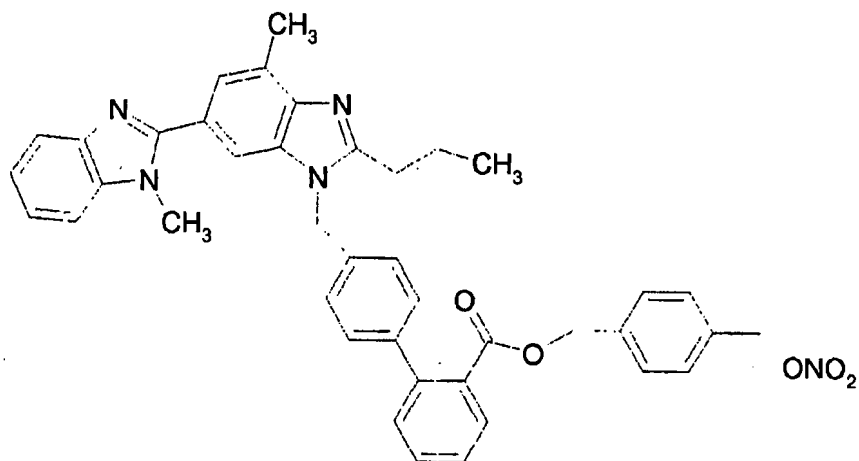
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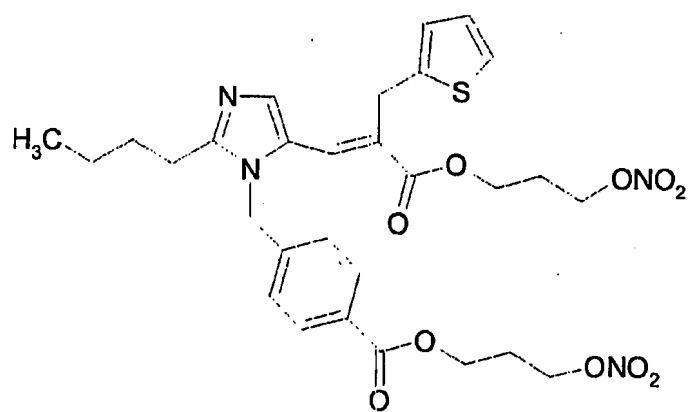
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(51)

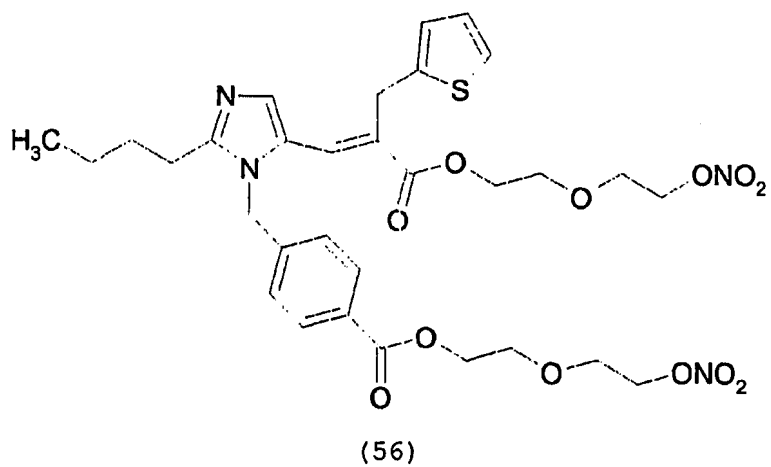
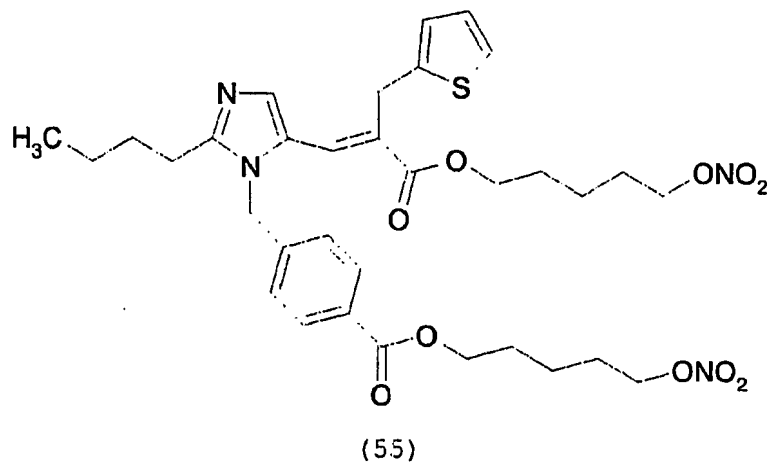
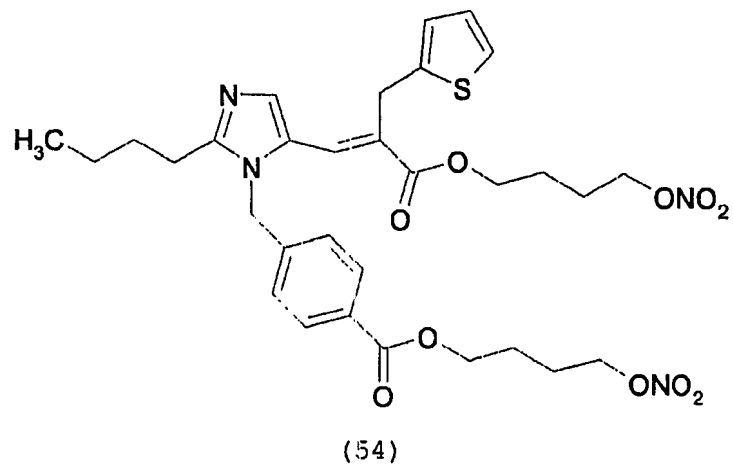


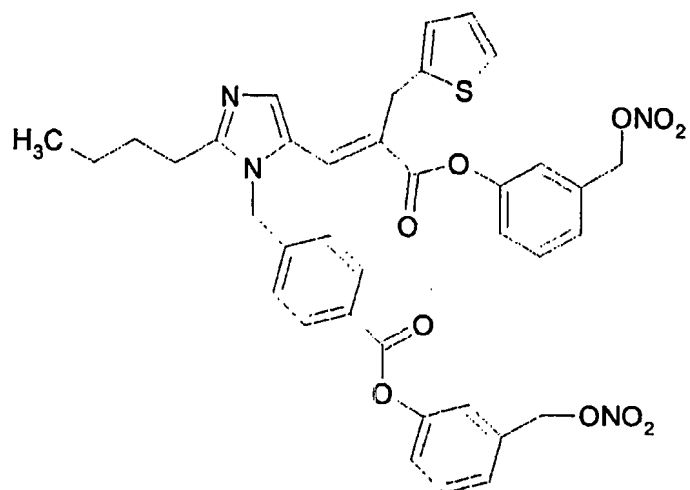
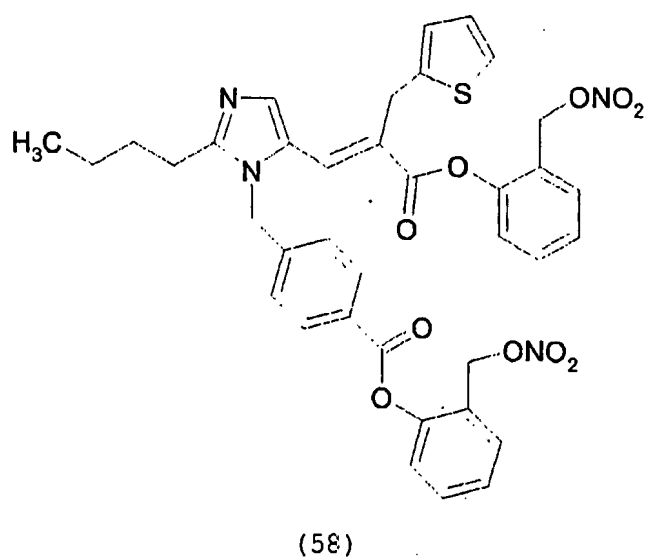
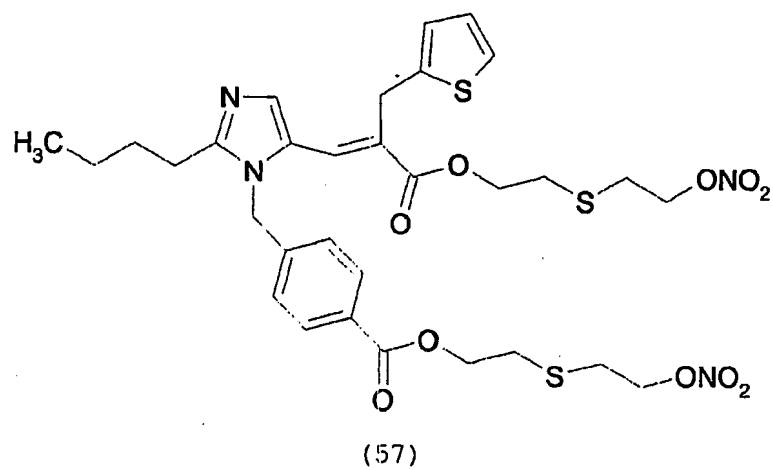
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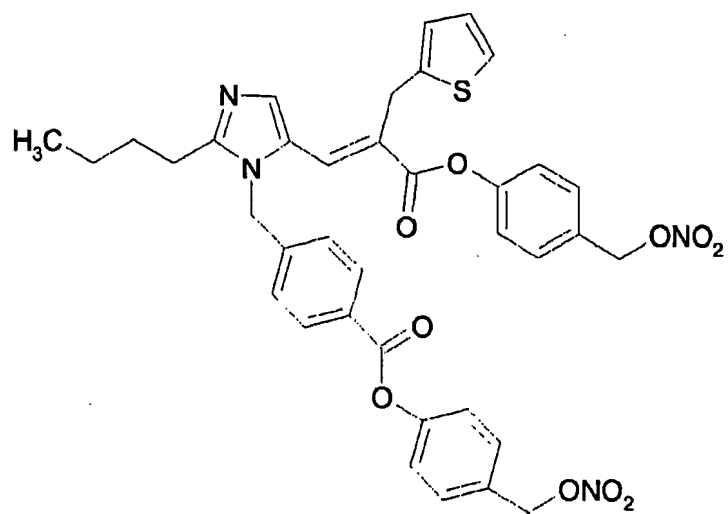
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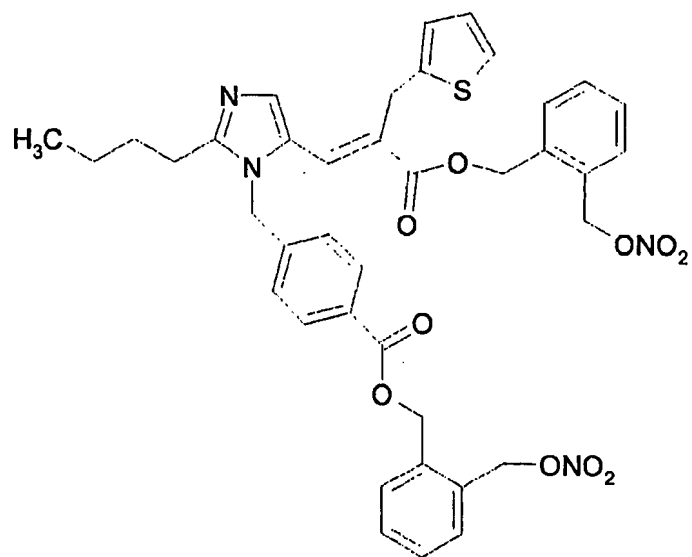




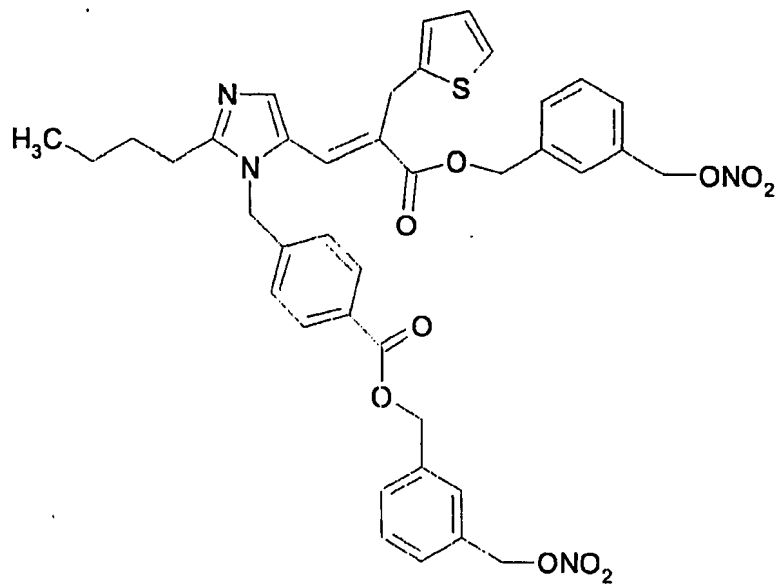
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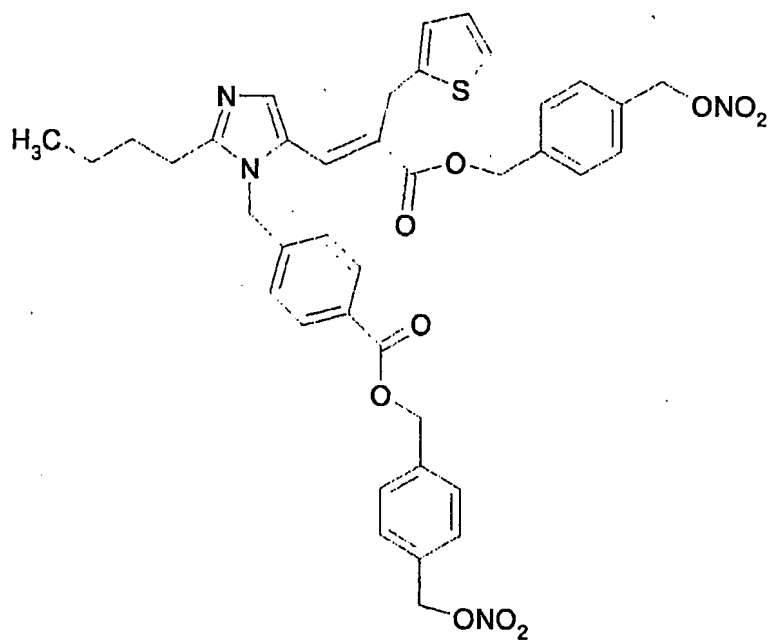
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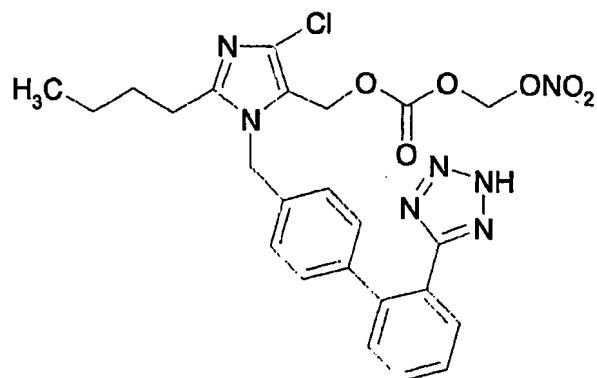
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(62)

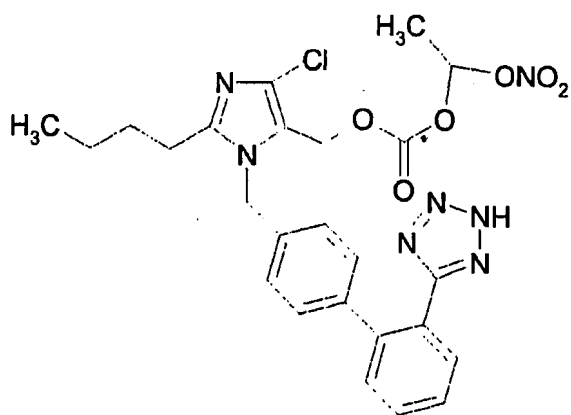


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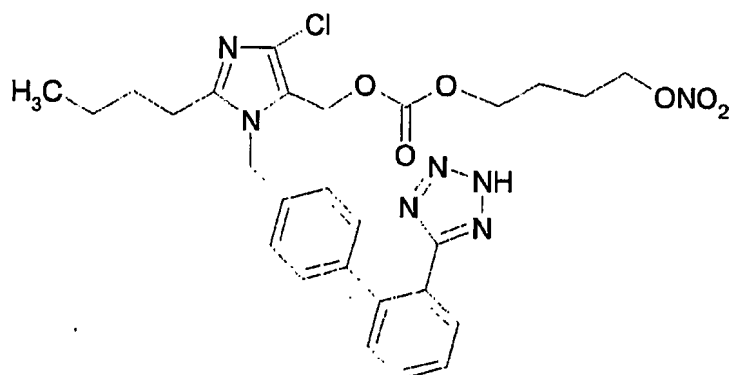


(64)

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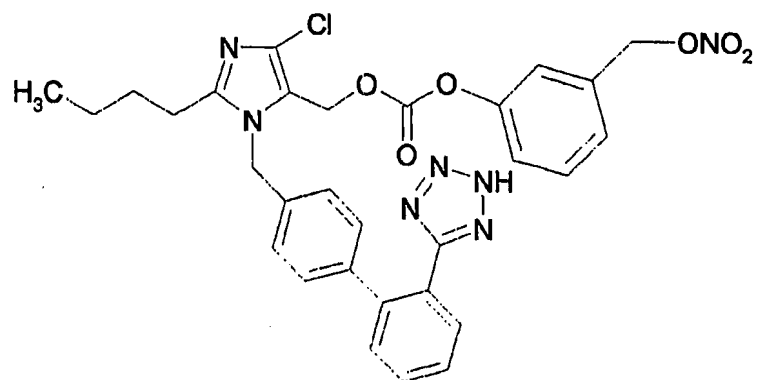


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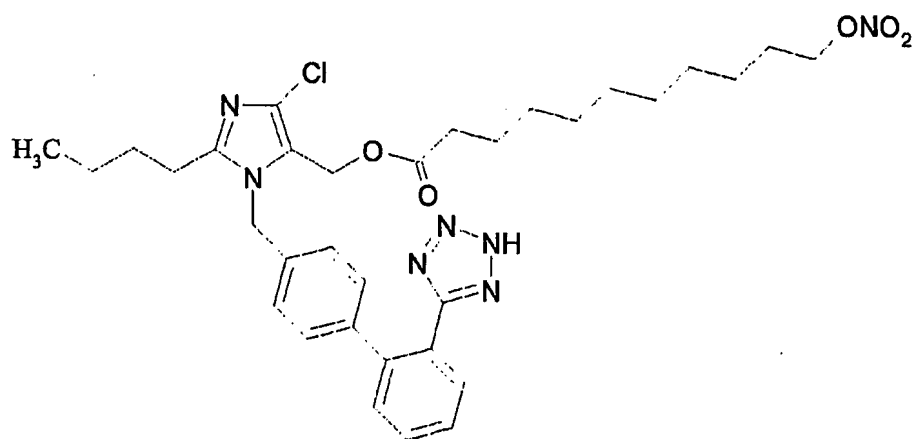


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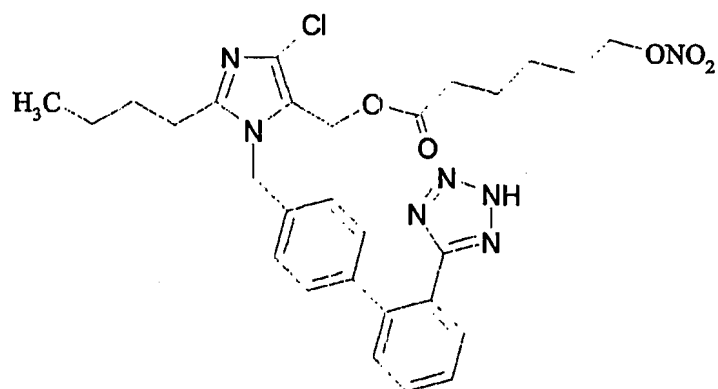


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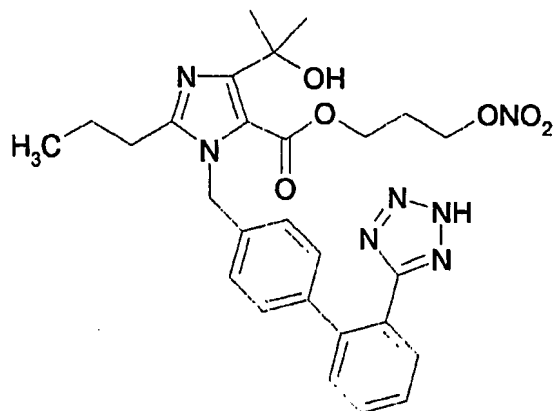


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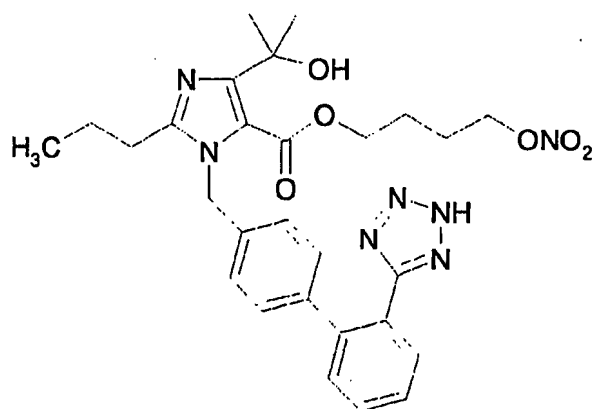
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(69)

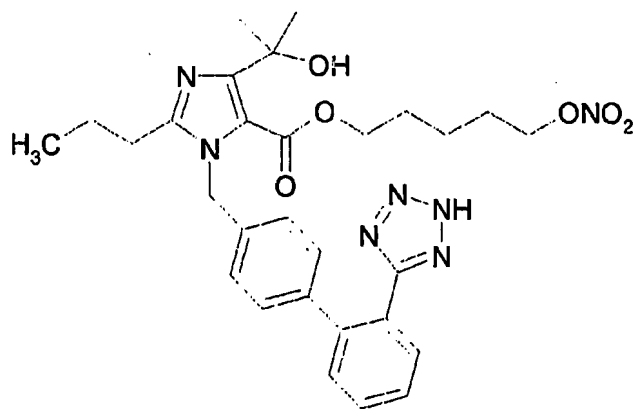


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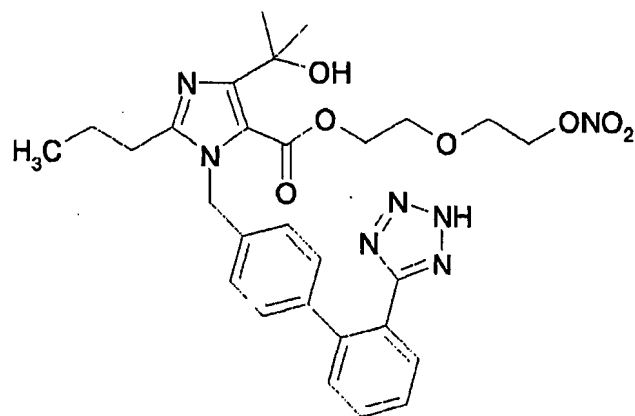


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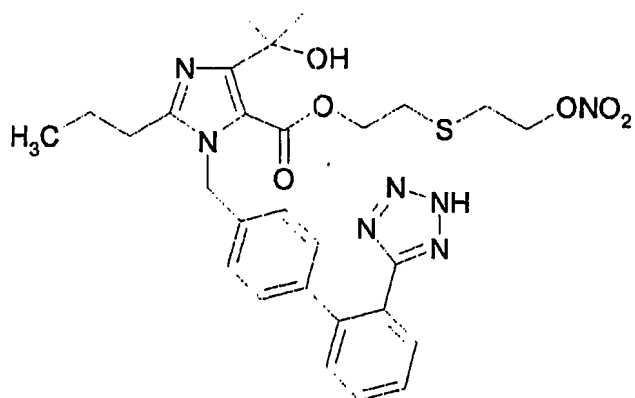
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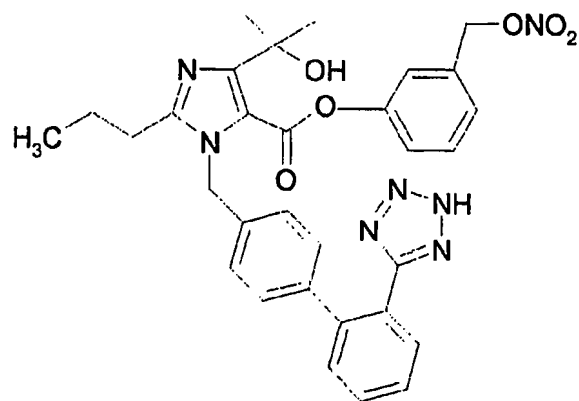
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(73)

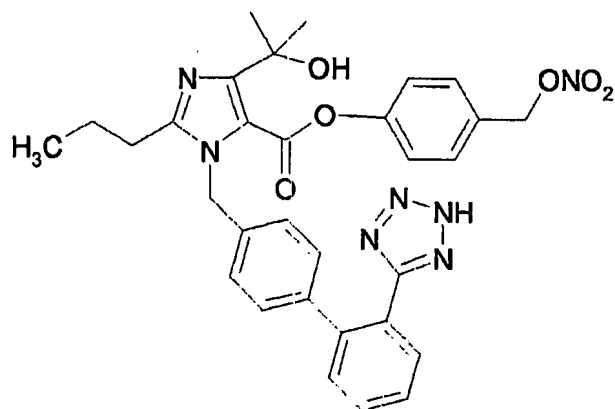


(74)

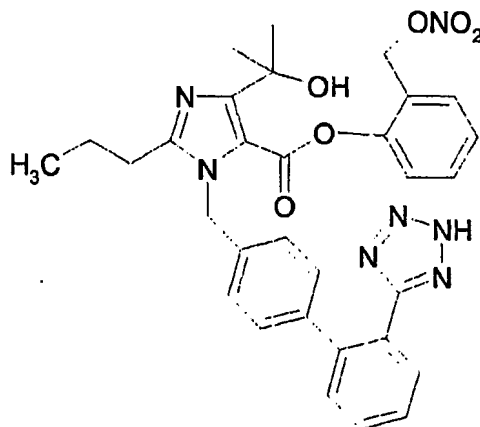


(75)

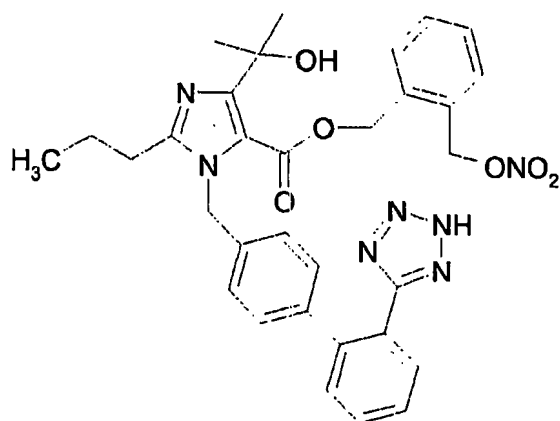




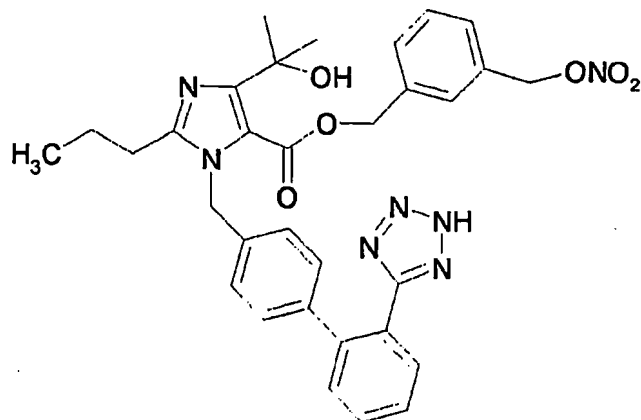
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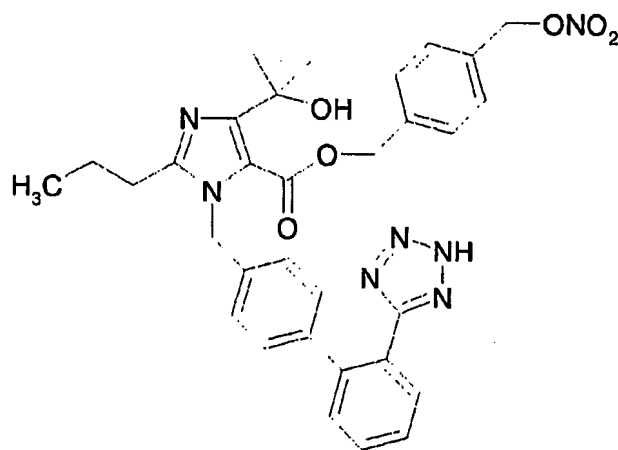
(77)



(78)



(79)



(80)

5

4. A compound of general formula (I) according to claims 1-3 for use as a medicament.

5. Use of a compound according to claims 1-3 for preparing  
10 a drug having anti-inflammatory, antithrombotic and antiplatelet activity.

6. Use of a compound according to claims 1-3, for preparing  
a drug that can be employed in the treatment or prophylaxis  
15 of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes.

7. Use of a compound according to claim 6, for preparing a drug that can be employed in the treatment or prophylaxis of heart failure, myocardial infarction, ischemic stroke, atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy, liver fibrosis and portal hypertension.
8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) or a salt or stereoisomer thereof according to claims 1-3.
9. A pharmaceutical composition according to claim 8 in a suitable form for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or iontophoresis devices.
10. Liquid or solid pharmaceutical composition for oral, parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually with enteric coating, powders, granules, gels, emulsions, solutions, suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or liposomes, containing a compound of formula (I) or a salt or stereoisomer thereof according to claims 1-3 and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition comprising a compound of general formula (I), at least a compound used to treat cardiovascular disease and a pharmaceutically acceptable carrier.

12. Pharmaceutical composition according to claim 11 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: ACE inhibitors,  
5 HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

10

13. A pharmaceutical kit comprising a compound of general formula (I) as defined in claim 1, a compound used to treat cardiovascular disease as combined preparation for simultaneous, separated, sequential use for the treatment  
15 of cardiovascular disease.

14. A pharmaceutical kit according to claim 13 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: ACE inhibitors, HMGCoA  
20 reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

25

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(54) Title: SELF-EMULSIFYING FORMULATIONS OF CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

(57) Abstract: CETP Inhibitors have improved solubility and bioavailability in a lipophilic vehicle comprising a digestible oil, a lipophilic solvent, or a surfactant. Preferred such compositions are self-emulsifying or self-microemulsifying, and comprise 1. a CETP inhibitor; 2. a cosolvent; 3. a surfactant having an HLB of 1 to 8; 4. a surfactant having an HLB of over 8 to 20; and 5. optionally, a digestible oil.

5                    **Self-emulsifying Formulations of Cholesteryl Ester**  
                      **Transfer Protein Inhibitors**

**Field Of The Invention**

10                This invention relates to encapsulated formulations of cholesterol ester transfer protein (CETP) inhibitors for use in mammals, especially humans, which formulations provide increased concentrations of CETP inhibitors for absorption, hence higher bioavailability.

**Background of the Invention**

15                CETP inhibitors, as a class, are characterized by high binding activity. Such CETP inhibitors are generally hydrophobic, however, with the consequence that they have extremely low aqueous solubility and have low oral bioavailability. Such compounds have generally proven to be difficult to formulate for oral administration such that high bioavailabilities are achieved.

20                Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of death in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular  
25                disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

                     Risk for development of this condition has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-cholesterol may be the most recognized form of dyslipidemia, it is by no means the only significant lipid-associated contributor to CHD. Low HDL-cholesterol is also a known risk factor for  
30                CHD (Gordon, D.J., et al., "High-density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

                     High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated, with the risk for developing  
35                cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

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Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal species, including humans, is to transfer cholesteryl ester and triglyceride  
5 between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

10 No wholly satisfactory HDL-elevating therapies exist. Niacin can significantly increase HDL, but has serious toleration issues that reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-cholesterol only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent that can significantly elevate plasma HDL levels, thereby reversing or slowing  
15 the progression of atherosclerosis.

CETP inhibitors have been developed that inhibit CETP activity, and thus, if present in the blood, should result in higher HDL cholesterol levels and lower LDL cholesterol levels. To be effective, such CETP inhibitors must be absorbed into the blood. Oral dosing of CETP inhibitors is preferred because to be effective such CETP  
20 inhibitors must be taken on a regular basis, such as daily. Accordingly, it is preferred that patients be able to take CETP inhibitors by oral dosing rather than by injection.

However, it has proven to be difficult to formulate CETP inhibitors for oral administration such that therapeutic blood levels are achieved. CETP inhibitors, in general, possess a number of characteristics that render them poorly bioavailable  
25 when dosed orally in a conventional manner. CETP inhibitors tend to be quite hydrophobic and extremely water insoluble, with solubility in aqueous solution of usually less than about 10 µg/ml and typically less than 1 µg/ml. Often the aqueous solubility of CETP inhibitors is less than 0.1 µg/ml. Indeed, the solubility of some CETP inhibitors is so low that it is in fact difficult to measure. Accordingly, when  
30 CETP inhibitors are dosed orally, concentrations of CETP inhibitor in the aqueous environment of the gastrointestinal tract tend to be extremely low, resulting in poor absorption from the GI tract to blood. The hydrophobicity of CETP inhibitors not only leads to low equilibrium aqueous solubility but also tends to make the drugs poorly wetting and slow to dissolve, further reducing their tendency to dissolve and be



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absorbed from the gastrointestinal tract. This combination of characteristics has resulted in the bioavailability for orally dosed conventional crystalline or amorphous forms of CETP inhibitors generally to be quite low, often having absolute bioavailabilities of less than 1%.

5           Various attempts have been made to improve the aqueous concentration of CETP inhibitors, but generally have met with limited success. Conventional methods of formulation do not provide sufficient solubilities and thus poor oral bioavailabilities have been obtained. Pre-dissolving CETP inhibitors in hydrophilic solvents such as acetone or PEG followed by delivery as a solution have failed due to inadequate  
10           solubility in the solvent or precipitation upon dilution into the aqueous medium. Suspensions of crystalline drug do not provide sufficient concentrations of drug in solution due to very low aqueous solubilities and therefore yield inadequate blood levels.

          One approach that has been disclosed to formulate CETP inhibitors is the  
15           formation of CETP solutions in lipids. Solutions in medium chain triglycerides have been of value either as oral solutions or encapsulated in softgels. However, the solubility (65 mg/mL or less) for some of the most potent and useful CETP inhibitors known to the inventors has limited the dose to 30 mg in a reasonable sized softgel. The efficacious dose is expected to be several multiples of this and therefore may  
20           require administration of more than 2 softgels per day.

          It has also been found that it is necessary to administer triglyceride solutions with food in order to achieve efficacious blood levels of CETP inhibitors. Food effects of 20-30x have been observed in man for some CETP inhibitors, with considerable variability between patients. The food effect is the ratio of plasma AUC values  
25           measured for administration of drug with a meal vs. administration in the fasted state. In addition, there is minimal CETP inhibition in the absence of food due to low fasted plasma exposure. As a result, labeling would need to indicate administration with food. This strong dependence of exposure on food could compromise the effectiveness of this medication in the treatment of atherosclerosis if there is a lack of  
30           compliance with labeling instructions.

          Therefore, there remains a need to develop oral formulations of CETP inhibitors that would reduce the food effect substantially, primarily by improving fasted exposure, thereby minimizing patient-to-patient variability in clinical outcome. An increase in the dose per capsule would also be a desirable improvement.

- Lack of mixing between oil formulations and the aqueous environment of the GI tract is known to lead to variable gastric emptying and thus variable absorption. A frequent means of increasing fasted bioavailability of hydrophobic drugs is to use a surfactant or combination of surfactants to produce an emulsion, which, if of sufficiently small particle size can lead to enhanced absorption of the drug. Lipid solutions containing surfactants that spontaneously form emulsions when mixed with an aqueous medium are referred to in the literature as self-emulsifying drug delivery systems (SEDDS) (S. Charman, et. al., Pharm Res., vol. 9, 87 (1992)). They are isotropic mixtures of oil, typically medium chain triglycerides, and non-ionic emulsifier that yield fine emulsions when gently mixed with aqueous fluid, such as in the stomach and intestine, and have the appropriate polarity for fast drug release (C. W. Pouton, Adv. Drug Deliv. Rev, vol. 25, 47 (1997); P.P. Constantinides, Pharm. Res., vol. 12, 1561 (1995); A. Humberstone and W. Charman, Adv. Drug Del. Rev., vol 25, 103 (1997)). Early SEDDS were defined as: forming an emulsion with particle size below 5 microns (S. Charman, et. al., Pharm Res., vol. 9, 87 (1992)) and utilized MIGLYOL<sup>®</sup> and a single surfactant, Tagat TO, which has an HLB (hydrophilic-lipophilic balance) of 10, to form a emulsion with a droplet size of 3 microns. Tagat is not available for human use as are other excipients with the appropriate properties.
- Much of the effort in both the open and patent literature has been invested in formulations of cyclosporin. A formulation of cyclosporin that was found to increase bioavailability by in situ generation of an emulsion utilized long chain triglyceride, a polyglycolized glyceride, and ethanol and was marketed as Sandimmune<sup>®</sup> (Cavanak (Sandoz)). See US 4,388,307 (1983). This had the disadvantage of considerable variability in oral bioavailability and PK profile. Subsequently, a self-microemulsifying system was developed (Meinzer, (Sandoz) WO 93/20833; Ritschel, Clin. Transplant., vol. 10, 364 (1996)) using polyethoxylated hydrogenated castor oil (Cremophor<sup>®</sup> RH40), corn oil mono-, di- and triglycerides, propylene glycol and ethanol. This softgel formulation, marketed as Neoral<sup>®</sup>, reduced variability in exposure and also reduced the moderate food effect (Mueller, Pharm. Res. vol 11, 151 (1994)).

Lipophilic solvents have been used in place of ethanol or propylene glycol which will not migrate to the shell and affect shell integrity and/or volatilize and thus impact on the concentration in the fill and on solubility. Triacetin has been used as a

lipophilic cosolvent for cyclosporin microemulsion preconcentrates with a long chain triglyceride and high HLB surfactant (Hong (Chong Kun Dang Corp.) WO 99/000002). It has also been used alone and in a mixture with propylene glycol dicaprylate/dicaprate and a high HLB surfactant for ketoprofen and related anti-inflammatory acids (Shelley and Wei (Scherer) WO 95/31979A).

US 5,993,858 discloses the use of an oil, high HLB surfactant, cosurfactant and triacetin as cosolvent for self-emulsifying formulations of hydrophobic drugs. Propylene carbonate has also been used as a lipophilic solvent for cyclosporin self-emulsifying systems (Woo (Novartis) WO 97/48410 and US 5,958,876 (1999)). Use of ethyl lactate as a cosolvent for cyclosporin formulations, including clinical evaluation, has also been reported (WO 00/40219).

#### Summary Of The Invention

This invention provides pharmaceutical compositions that are liquid solutions, suspensions, and (oil-in-water) emulsions of CETP inhibitors, said solutions being orally administrable. The solutions or dispersions may be administered, for example, as fill in encapsulated dosage forms such as hard or soft gelatin capsules. The CETP inhibitors can be dissolved or dispersed in a variety of lipophilic vehicles, as further described and discussed below, such as digestible oils, solvents and surfactants, including mixtures of any two or more of the aforementioned vehicles.

Reference to a compositional component such as a "digestible oil", to a "surfactant" and so forth, shall be understood as including mixtures of such components such as mixtures of digestible oils and surfactants.

In a first embodiment, the CETP inhibitor is dissolved or dispersed in a digestible oil such as a medium chain triglyceride oil or a mixture of digestible oils.

In a second embodiment, the CETP inhibitor is dissolved or dispersed in a digestible oil with one or more high HLB surfactants. The aforementioned solution or dispersion containing a high HLB surfactant or surfactant mixture may optionally contain one or more low HLB surfactants.

In a third embodiment, the CETP inhibitor is dissolved in a pharmaceutically acceptable lipophilic solvent optionally containing a digestible oil or digestible oil mixture. The CETP inhibitor solvent solution or dispersion or solvent/digestible oil solution or dispersion may optionally contain one or more high HLB surfactants and/or

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one or more low HLB surfactants.

The presence of one or more surfactants can, upon contacting the pharmaceutical composition with water, yield an emulsion that is either preformed by mixing with an aqueous phase or that is generated in vivo by contacting the aqueous fluids of the gastrointestinal tract. Formation of an emulsion can improve fasted bioavailability and thus reduce the food effect in man (i.e., the effect of food upon absorption and/or bioavailability of a drug). It can also allow the oil to be consumed as a beverage in addition to being administered in capsules. Use of surfactants to provide an emulsion can also be of value for increasing exposures in toxicology species. Combination of a digestible oil with a cosolvent can have the advantage of higher solubility and thus a higher dose in a given volume of formulation than is obtainable with the digestible oil alone. It is advantageous for bioavailability to have the entire dose dissolved. The presence of a third component in any of the above embodiments may also improve miscibility between the first two components.

Thus, in a first embodiment, the invention provides an orally administrable pharmaceutical composition comprising a CETP inhibitor and a lipophilic vehicle selected from a digestible oil, a lipophilic solvent (also referred to herein as a "cosolvent", whether or not another solvent is in fact present), a lipophilic surfactant, and mixtures of any two or more thereof. Preferred embodiments include a CETP inhibitor and: (1) the combination of a pharmaceutically acceptable digestible oil and a surfactant; (2) the combination of a pharmaceutically acceptable digestible oil and a lipophilic solvent which is miscible therewith; and (3) the combination of a pharmaceutically acceptable digestible oil, a lipophilic solvent, and a surfactant.

In a particularly preferred embodiment, the invention provides a composition of matter for increasing the oral bioavailability of a CETP inhibitor. The composition comprises:

1. a CETP inhibitor;
2. a cosolvent;
3. a surfactant having an HLB of from 1 to not more than 8;
4. a surfactant having an HLB of over 8 up to 20; and
5. optionally, a digestible oil.

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In such formulations, all of the excipients are pharmaceutically acceptable. The above composition is sometimes referred to herein as a "pre-concentrate", in reference to its function of forming a stable emulsion when gently mixed with water or other aqueous medium, usually gastrointestinal fluids. It is also referred to herein as a "fill", referring to its utility as a fill for a softgel capsule.

Reference herein is frequently made to a softgel as a preferred dosage form for use with this invention, "softgel" being an abbreviation for soft gelatin capsules. It is understood that when reference is made to the term "softgel" alone, it shall be understood that the invention applies equally to all types of gelatin and non-gelatin capsules, regardless of hardness, softness, and so forth.

A cosolvent means a solvent in which the CETP inhibitor of interest is highly soluble, having, for any given CETP inhibitor, a solubility of at least 150 mg/mL.

As noted above, and as discussed further below, a digestible oil can form a part of the pre-concentrate. If no other component of the pre-concentrate is capable of functioning as an emulsifiable oily phase, a digestible oil can be included as the oil which acts as a solvent for the CETP inhibitor and which disperses to form the (emulsifiable) oil droplet phase once the pre-concentrate has been added to water. Some surfactants can serve a dual function, however, i.e., that of acting as a surfactant and also as a solvent and an oily vehicle for forming an oil-in-water emulsion. In the event such a surfactant is employed, and, depending on the amount used, a digestible oil may be required in less of an amount, or not required at all.

The pre-concentrate can be self-emulsifying or self-microemulsifying.

The term "self-emulsifying" refers to a formulation which, when diluted by a factor of at least 100 by water or other aqueous medium and gently mixed, yields an opaque, stable oil/water emulsion with a mean droplet diameter less than about 5 microns, but greater than 100 nm, and which is generally polydisperse. Such an emulsion is stable for at least several (i.e., for at least 6) hours, meaning there is no visibly detectable phase separation and that there is no visibly detectable crystallization of CETP inhibitor.

The term "self-microemulsifying" refers to a pre-concentrate which, upon at least 100 x dilution with an aqueous medium and gentle mixing, yields a non-opaque, stable oil/water emulsion with an average droplet size of about 1 micron or less, said average particle size preferably being less than 100 nm. The particle size is primarily

unimodal. Most preferably the emulsion is transparent and has a unimodal particle size distribution with a mean diameter less than 50 nm as determined, for example, by dynamic light scattering. The microemulsion is thermodynamically stable and without any indication of crystallization of CETP inhibitor.

5           “Gentle mixing” as used above is understood in the art to refer to the formation of an emulsion by gentle hand (or machine) mixing, such as by repeated inversions on a standard laboratory mixing machine. High shear mixing is not required to form the emulsion. Such pre-concentrates generally emulsify nearly spontaneously when introduced into the human (or other animal) gastrointestinal tract.

10           The term “CETP inhibitor” implies any such compound that is sparingly or poorly water soluble. Generally, and as mentioned above, such compounds exhibit an aqueous solubility (e.g., in water) of less than about 10 µg/mL measured at about 22°C and at a physiologically relevant pH of from 1 through 8.

          Combinations of 2 surfactants, one being a low HLB surfactant with an HLB of  
15 1 to 8, the other being a high HLB surfactant with a higher HLB of over 8 to 20, preferably 9 to 20, can be employed to create the right conditions for efficient emulsification. The HLB, an acronym for “hydrophobic-lipophilic balance”, is a rating scale which can range from 1-20 for non-ionic surfactants. The higher the HLB, the more hydrophilic the surfactant. Hydrophilic surfactants (HLB ca. 8 -20), when used  
20 alone, provide fine emulsions which are, advantageously, more likely to empty uniformly from the stomach and provide a much higher surface area for absorption. Disadvantageously, however, limited miscibility of such high HLB surfactants with oils can limit their effectiveness, and thus a low HLB, lipophilic surfactant (HLB ca. 1-8) is also included. This combination of surfactants can also provide superior  
25 emulsification. A combination of a medium chain triglyceride (such as Miglyol® 812), Polysorbate 80 (HLB 15) and medium chain mono/diglycerides (Capmul® MCM, HLB =6) was found to be as efficient as Miglyol® 812 and a surfactant with an HLB of 10 (Labrafac® CM). N.H. Shah et al. Int. J. Pharm., vol 106, 15 (1994). The advantages of using combinations of high and low HLB surfactants for self-emulsifying systems,  
30 including promotion of lipolysis, have been demonstrated by Lacy, US 6,096,338.

Detailed Description

Suitable digestible oils, which can be used alone as the vehicle or in a vehicle which includes a digestible oil as part of a mixture, include medium chain triglycerides (MCT, C6-C12) and long chain triglycerides (LCT, C14-C20) and mixtures of mono-,  
5 di-, and triglycerides, or lipophilic derivatives of fatty acids such as esters with alkyl alcohols. Examples of preferred MCT's include fractionated coconut oils, such as Miglyol® 812 which is a 56% caprylic (C8) and 36% capric (C10) triglyceride, Miglyol® 810 (68% C8 and 28% C10), Neobee® M5, Captex® 300, Captex® 355, and Crodamol® GTCC. The Miglyols are supplied by Condea Vista Inc. (Huls), Neobee®  
10 by Stepan Europe, Voreppe, France, Captex® by Abitec Corp., and Crodamol® by Croda Corp. Examples of LCTs include vegetable oils such as soybean, safflower, corn, olive, cottonseed, arachis, sunflowerseed, palm, or rapeseed. Examples of fatty acid esters of alkyl alcohols include ethyl oleate and glyceryl monooleate. Of the digestible oils MCT's are preferred, and Miglyol® 812 is most preferred.

15 The vehicle may also be a pharmaceutically acceptable solvent, for use alone, or as a cosolvent in a mixture. Suitable solvents include any solvent that is used to increase solubility of the CETP inhibitor in the formulation in order to allow delivery of the desired dose per dosing unit. It is not generally possible to predict the solubility of CETP inhibitors in the individual solvents, but such can be easily determined by "trial  
20 runs". Suitable solvents include triacetin (1,2,3-propanetriyl triacetate or glyceryl triacetate available from Eastman Chemical Corp.) or other polyol esters of fatty acids, trialkyl citrate esters, propylene carbonate, dimethylisosorbide, ethyl lactate, N-methyl pyrrolidones, transcitol, glycofurol, peppermint oil, 1,2- propylene glycol, ethanol, and polyethylene glycols. Preferred as solvents are triacetin, propylene carbonate  
25 (Huntsman Corp.), transcitol (Gattefosse), ethyl lactate (Purac, Lincolnshire, NE) and dimethylisosorbide (sold under the registered trademark ARLASOLVE DMI, ICI Americas). A hydrophilic solvent is more likely to migrate to the capsule shell and soften the shell, and, if volatile, its concentration in the composition can be reduced, but with a potential negative impact on active component (CETP inhibitor) solubility.  
30 More preferred are the lipophilic solvents triacetin, ethyl lactate and propylene carbonate. Most preferred is triacetin.

Hydrophilic surfactants having an HLB of 8-20, preferably having an HLB greater than 10, are particularly effective at reducing emulsion droplet particle size. Suitable choices include nonionic surfactants such as polyoxyethylene 20 sorbitan

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monooleate, polysorbate 80, sold under the trademark TWEEN 80, available commercially from ICI; polyoxyethylene 20 sorbitan monolaurate (Polysorbate 20, TWEEN 20); polyethylene (40 or 60) hydrogenated castor oil (available under the registered trademarks CREMOPHOR® RH40 and RH60 from BASF); polyoxyethylene  
 5 (35) castor oil (CREMOPHOR® EL); polyethylene (60) hydrogenated castor oil (Nikkol® HCO-60); alpha tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS); glyceryl PEG 8 caprylate/caprate (available commercially under the registered trademark LABRASOL® from Gattefosse); PEG 32 glyceryl laurate (sold commercially under the registered trademark GELUCIRE® 44/14 by Gattefosse), polyoxyethylene  
 10 fatty acid esters (available commercially under the registered trademark MYRJ from ICI), polyoxyethylene fatty acid ethers (available commercially under the registered trademark BRIJ from ICI). Preferred are Polysorbate 80, CREMOPHOR® RH40 (BASF), and Vitamin E TPGS (Eastman). Most preferred are Polysorbate 80 and CREMOPHOR® RH40.

15 Lipophilic surfactants having an HLB of less than 8 are useful for achieving a balance of polarity to provide a stable emulsion, and have also been used to reverse the lipolysis inhibitory effect of hydrophilic surfactants. Suitable lipophilic surfactants include mono and diglycerides of capric and caprylic acid under the following registered trademarks: Capmul® MCM, MCM 8, and MCM 10, available commercially  
 20 from Abitec; and Imwitor® 988, 742 or 308, available commercially from Condea Vista; polyoxyethylene 6 apricot kernel oil, available under the registered trademark Labrafil® M 1944 CS from Gattefosse; polyoxyethylene corn oil, available commercially as Labrafil® M 2125; propylene glycol monolaurate, available commercially as Lauroglycol from Gattefosse; propylene glycol dicaprylate/caprate available  
 25 commercially as Captex® 200 from Abitec or Miglyol® 840 from Condea Vista, polyglyceryl oleate available commercially as Plurol oleique from Gattefosse, sorbitan esters of fatty acids (e.g. Span® 20, Crill® 1, Crill® 4, available commercially from ICI and Croda), and glyceryl monooleate (Maisine, Peceol). Preferred from this class are Capmul® MCM (Abitec Corp.) and Labrafil® M1944 CS (Gattefosse). Most preferred  
 30 is Capmul® MCM.

In addition to the main liquid formulation ingredients previously noted, other stabilizing additives, as conventionally known in the art of softgel formulation, can be introduced to the fill as needed, usually in relatively small quantities, such as antioxidants (BHA, BHT, tocopherol, propyl gallate, etc.) and other preservatives such



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as benzyl alcohol or parabens.

The composition can be formulated as a fill encapsulated in a soft gelatin capsule, a hard gelatin capsule with an appropriate seal, a non-gelatin capsule such as a hydroxypropyl methylcellulose capsule or an oral liquid or emulsion by methods commonly employed in the art. The fill is prepared by mixing the excipients and CETP inhibitor with heating if required.

The ratio of CETP inhibitor, digestible oil, cosolvent, and surfactants depends upon the efficiency of emulsification and the solubility, and the solubility depends on the dose per capsule that is desired. A self-emulsifying formulation is generally useful if the primary goals are to deliver a high dose per softgel (at least 60 mg) with, generally, a much lower food effect than with an oil solution alone. In general, softgel preconcentrates having solubilities of CETP inhibitor of at least 140 mg/mL in the preconcentrate, and thus requiring higher amounts of cosolvent and lower levels of surfactants and oil, are preferred.

In general, the following ranges, in weight percent, of the components for a self-emulsifying formulation of CETP inhibitors are:

- 1 - 50 % CETP inhibitor
- 5 - 60 % cosolvent
- 5 - 75 % high HLB surfactant
- 5 - 75 % low HLB surfactant

Preferred ranges which have advantageously low food effects include those stated immediately below:

- 1 - 33 % CETP inhibitor
- 0 - 30 % digestible oil
- 15 - 55 % cosolvent
- 5 - 40 % high HLB surfactant
- 10 - 50 % low HLB surfactant

More preferred ranges include

- 1 - 25 % CETP inhibitor
- 10 - 25 % digestible oil
- 20 - 35 % cosolvent

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10 - 30 % high HLB surfactant

15 - 35 % low HLB surfactant

5 If a specific goal is a minimal food effect, then a self-microemulsifying formulation is advantageous. Such formulations generally require relatively high levels of surfactants and a reduced amount of cosolvent. These formulations can, however, result in lower solubilities and, accordingly, a lower dose per capsule. These formulations have been found to increase fasted exposure.

10 General ranges, in weight percent, for the components for a self-microemulsifying formulation of CETP inhibitors are

1 - 40% CETP inhibitor

5 - 65 % digestible oil

5 - 60 % cosolvent

10 - 75 % high HLB surfactant

15 5 - 75 % low HLB surfactant

Preferred ranges include those which follow

1- 20 % CETP inhibitor

5 - 30 % digestible oil

5 - 45 % cosolvent

20 30 - 55%, high HLB surfactant

10 - 40 %, low HLB surfactant

Specific examples of preferred formulations include:

A composition comprising

25 a compound which is [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; or a compound which is [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester; or a compound which is [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-

30 dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

a cosolvent;

a high HLB surfactant;

a low HLB surfactant; and

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optionally, a digestible oil.

A more preferred composition is that noted immediately above, wherein

said cosolvent is triacetin or ethyl lactate;

said high HLB surfactant comprises polysorbate 80 or a polyethylene

5 hydrogenated castor oil;

said low HLB surfactant comprises a mixture of mono- and diglycerides of capric and caprylic acids;

said digestible oil comprises a medium chain triglyceride, wherein each of the three hydrocarbon chains therein is predominantly C6-C12.

10

A more specific preferred composition is that noted immediately above, which comprises, by weight:

5 -25% of said CETP inhibitor;

10-25% of said digestible oil;

15 20-35% of said cosolvent:

10-35% of said high HLB surfactant; and

10-35% of said low HLB surfactant;

A still more specific preferred embodiment is that noted immediately above which

20 comprises, by weight:

8-12% of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

10-20% of said digestible oil;

25-35% of said cosolvent which comprises triacetin:

25 10-30% of said high HLB surfactant which comprises polysorbate 80; and

15-35% of said low HLB surfactant which comprises a mixture of medium chain mono- and di-glycerides.

Another still more specific preferred embodiment is one, which comprises, by weight:

30 8-12% of [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

10-20% of said digestible oil;

25-35% of said cosolvent which comprises triacetin;

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10-30% of said high HLB surfactant which comprises a polyethylene (40)  
hydrogenated castor oil;

15-35% of said low HLB surfactant, which comprises a mixture of medium  
chain mono- and di-glycerides.

5

Another still more specific preferred embodiment is one which comprises, by weight

8-25% of [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-  
2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

10-25% of digestible oil;

10

20-35% of said cosolvent which comprises triacetin;

10-30% of said high HLB surfactant which comprises polysorbate 80; and

15-35% of said low HLB surfactant which comprises a mixture of medium chain  
mono- and di-glycerides.

As indicated by the broadest range above, the digestible oil may be optionally  
omitted in order to further increase the amount of cosolvent and, therefore, solubility  
of the CETP inhibitor in the pre-concentrate.

In addition to the main softgel capsule ingredients previously noted, other  
stabilizing additives, as conventionally known in the art of softgel formulation, can be  
introduced to the fill as needed, usually in relatively small quantities, such as  
antioxidants (BHA, BHT, tocopherol, propyl gallate, etc.) and other preservatives such  
as benzyl alcohol or parabens.

The composition can be formulated as a fill encapsulated in a soft gelatin  
capsule, a hard gelatin capsule with an appropriate seal, a non-gelatin capsule such  
as a hydroxypropyl methylcellulose capsule or an oral liquid or emulsion by methods  
commonly employed in the art. The fill is prepared by mixing the excipients and CETP  
inhibitor with heating if required.

Preferred embodiments comprise a CETP inhibitor with:

30

(a) solubility less than 10 µg/ml;

(b) c log P greater than 5; and/or

(c) dose greater than 10 mg, preferably at least 30 mg.

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The invention is not limited by any particular structure or group of CETP inhibitors. Rather, the invention has general applicability to CETP inhibitors as a class, the class tending to be composed of compounds having low solubility. Compounds which may be the subject of the invention may be found in a number of patents and published applications, including DE 19741400 A1; DE 19741399 A1; WO 9914215 A1; WO 9914174; DE 19709125 A1; DE 19704244 A1; DE 19704243 A1; EP 818448 A1; WO 9804528 A2; DE 19627431 A1; DE 19627430 A1; DE 19627419 A1; EP 796846 A1; DE 19832159; DE 818197; DE 19741051; WO 9941237 A1; WO 9914204 A1; WO 9835937 A1; JP 11049743; WO 200018721; WO 200018723; WO 200018724; WO 200017164; WO 200017165; WO 200017166; EP 992496; and EP 987251, all of which are hereby incorporated by reference in their entirety.

Oral delivery of many CETP inhibitors is particularly difficult because their aqueous solubility is usually extremely low, typically being less than 2  $\mu\text{g/ml}$ , often being less than 0.1  $\mu\text{g/ml}$ . Such low solubilities are a direct consequence of the particular structural characteristics of species that bind to CETP and thus act as CETP inhibitors. This low solubility is primarily due to the hydrophobic nature of CETP inhibitors. Log P, defined as the base 10 logarithm of the ratio of the drug concentration in octanol to the drug concentration in water in a partitioning experiment, is a widely accepted measure of hydrophobicity. In general, Log P values for CETP inhibitors are greater than 4 and are often greater than 5 to 7. This property may also be calculated from the structure of the molecule and is designated "cLog P.". The calculation of cLog P values from chemical structures is given in Leo, A.J.; "Calculating log P from structures", Chem. Rev. 1993, 93, 1281. Thus, the hydrophobic and insoluble nature of CETP inhibitors as a class pose a particular challenge for oral delivery. Achieving therapeutic drug levels in the blood by oral dosing of practical quantities of drug generally requires a large enhancement in drug concentrations in the gastrointestinal fluid and a resulting large enhancement in bioavailability.

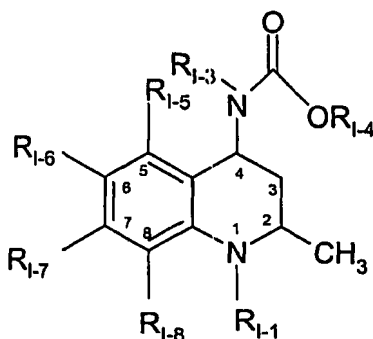
The formulations of this invention will be administered in such an amount that an effective dose of the CETP inhibitor of interest is administered to the patient. The amount of CETP inhibitor will generally be known or determined by the attending physician. Thus the amount or volume of preconcentrate administered will be determined by the amount of CETP inhibitor prescribed and/or otherwise desired as a

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dose and the solubility of the CETP in the preconcentrate. In general, an effective dose for most CETP inhibitors is in the range of from 5 to 500 mg, preferably 10-300 mg, more preferably 10-200 mg per day, in single or divided doses. The compositions of the invention are pre-concentrates for emulsification which are generally

5 administered orally, in soft or hard gelatin capsules, gelatin encapsulation technology being well known to the pharmaceutical arts. Such pre-concentrates can also be administered in aqueous oral emulsions by adding the pre-concentrate to water or other aqueous liquid (e.g., soda). They can be mixed with an aqueous liquid and sold as pre-formed emulsions, or added to food such as ice cream.

10 Turning now to the chemical structures of specific CETP inhibitors, one class of CETP inhibitors that finds utility with the present invention consists of oxy substituted 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines having the Formula I



15

Formula I

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

wherein  $R_{I-1}$  is hydrogen,  $Y_1$ ,  $W_1-X_1$ ,  $W_1-Y_1$ ;

20 wherein  $W_1$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

$X_1$  is  $-O-Y_1$ ,  $-S-Y_1$ ,  $-N(H)-Y_1$  or  $-N-(Y_1)_2$ ;

wherein  $Y_1$  for each occurrence is independently  $Z_1$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be

25 replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo,

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said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $Z_i$ ;

wherein  $Z_i$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $Z_i$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxyl,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxyl,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

$R_{4-3}$  is hydrogen or  $Q_i$ ;

wherein  $Q_i$  is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_i$ ;

wherein  $V_i$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $V_i$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carbamoyl, mono-N- or di-N,N- $(C_1-C_6)$

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alkylcarbamoyl, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituents are also optionally substituted with from one to nine fluorines;

R<sub>4</sub> is Q<sub>1-1</sub> or V<sub>1-1</sub>

wherein Q<sub>1-1</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>1-1</sub>;

wherein V<sub>1-1</sub> is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V<sub>1-1</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, nitro, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-substituted with oxo, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein either R<sub>1-3</sub> must contain V<sub>1</sub> or R<sub>4</sub> must contain V<sub>1-1</sub>; and R<sub>1-5</sub>, R<sub>1-6</sub>, R<sub>1-7</sub> and R<sub>1-8</sub> are each independently hydrogen, hydroxy or oxy wherein said oxy is substituted with T<sub>1</sub> or a partially saturated, fully saturated or fully unsaturated one to twelve membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with T<sub>1</sub>;



wherein  $T_1$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken  
5 independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $T_1$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-  
10 N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines.

15 Compounds of Formula I are disclosed in commonly assigned pending U.S. Patent Application Serial No. 09/390,731, the complete disclosure of which is herein incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula I:

20

[2R,4S] 4-[(3,5-dichloro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

25

[2R,4S] 4-[(3,5-dinitro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

30

[2R,4S] 4-[(2,6-dichloro-pyridin-4-ylmethyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

35

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

40

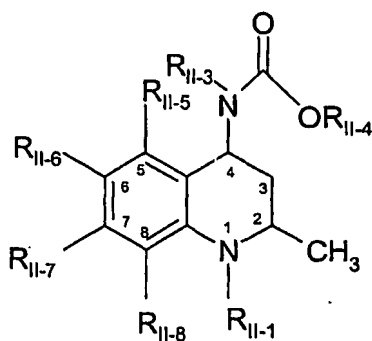
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

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- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-ethoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- 5 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoro-ethylester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- 10 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
- 15 [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester;
- [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester;
- 20 [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-[1-(2-ethyl-butyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid methyl ester, hydrochloride

- 25 Another class of CETP inhibitors that finds utility with the present invention consists of 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines, having the Formula II



- 30 Formula II

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

wherein  $R_{II-1}$  is hydrogen,  $Y_{II}$ ,  $W_{II}-X_{II}$ ,  $W_{II}-Y_{II}$ ;

wherein  $W_{II}$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

- 35  $X_{II}$  is  $-O-Y_{II}$ ,  $-S-Y_{II}$ ,  $-N(H)-Y_{II}$  or  $-N-(Y_{II})_2$ ;

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wherein  $Y_{ii}$  for each occurrence is independently  $Z_{ii}$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $Z_{ii}$ ;

$Z_{ii}$  is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $Z_{ii}$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl is also optionally substituted with from one to nine fluorines;

$R_{i1-3}$  is hydrogen or  $Q_{ii}$ ;

wherein  $Q_{ii}$  is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{ii}$ ;

wherein  $V_{ii}$  is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected

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independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

- 5            wherein said  $V_{II}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally  
10 mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino or said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituents are optionally substituted with from one to nine fluorines;

$R_{II-4}$  is  $Q_{II-1}$  or  $V_{II-1}$

- 15            wherein  $Q_{II-1}$  a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said  
20 carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{II-1}$ ;

- wherein  $V_{II-1}$  is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently  
25 from oxygen, sulfur and nitrogen;

- wherein said  $V_{II-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent is  
30 optionally substituted with from one to nine fluorines;

             wherein either  $R_{II-3}$  must contain  $V_{II}$  or  $R_{II-4}$  must contain  $V_{II-1}$ ; and

$R_{II-5}$ ,  $R_{II-6}$ ,  $R_{II-7}$  and  $R_{II-8}$  are each independently hydrogen, a bond, nitro or halo wherein said bond is substituted with  $T_{II}$  or a partially saturated, fully saturated or fully unsaturated  $(C_1-C_{12})$  straight or branched carbon chain wherein carbon may optionally

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be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-  
 5 substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon is optionally mono-substituted with T<sub>II</sub>;

wherein T<sub>II</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two  
 10 fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said T<sub>II</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-  
 15 C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine  
 20 fluorines;

provided that at least one of substituents R<sub>II-6</sub>, R<sub>II-8</sub>, R<sub>II-7</sub> and R<sub>II-8</sub> is not hydrogen and is not linked to the quinoline moiety through oxy.

Compounds of Formula II are disclosed in commonly assigned pending U.S. Patent 6,147,090 the complete disclosure of which is herein incorporated by reference.

25 In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula II:

- 30 [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- 35 [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2,6,7-trimethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

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[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-diethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

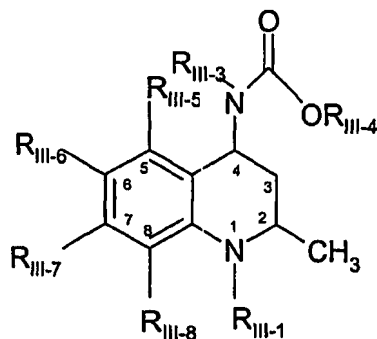
5 [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-ethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

10

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

15 Another class of CETP inhibitors that finds utility with the present invention consists of annulated 4-carboxyamino-2-methyl-1,2,3,4,-tetrahydroquinolines, having the Formula III



20

Formula III

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

wherein  $R_{III-1}$  is hydrogen,  $Y_{III}$ ,  $W_{III}-X_{III}$ ,  $W_{III}-Y_{III}$ ;

wherein  $W_{III}$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

25  $X_{III}$  is  $-O-Y_{III}$ ,  $-S-Y_{III}$ ,  $-N(H)-Y_{III}$  or  $-N-(Y_{III})_2$ ;

$Y_{III}$  for each occurrence is independently  $Z_{III}$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and  
30 nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo,

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said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z<sub>III</sub>;

wherein Z<sub>III</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected

5 independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said Z<sub>III</sub> substituent is optionally mono-, di- or tri-substituted

10 independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-  
15 C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to nine fluorines; R<sub>III-3</sub> is hydrogen or Q<sub>III</sub>;

wherein Q<sub>III</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from

20 oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>III</sub>;

25 wherein V<sub>III</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected  
30 independently from nitrogen, sulfur and oxygen;

wherein said V<sub>III</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarboxamoyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-

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C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino or said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl are optionally substituted with from  
 5 one to nine fluorines;

R<sub>III-4</sub> is Q<sub>III-1</sub> or V<sub>III-1</sub>;

wherein Q<sub>III-1</sub> a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from  
 10 oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with

15 V<sub>III-1</sub>;

wherein V<sub>III-1</sub> is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V<sub>III-1</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted  
 20 independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, nitro, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-substituted with oxo, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent optionally having from one to nine fluorines;

wherein either R<sub>III-3</sub> must contain V<sub>III</sub> or R<sub>III-4</sub> must contain V<sub>III-1</sub>; and  
 25 R<sub>III-5</sub> and R<sub>III-6</sub>, or R<sub>III-6</sub> and R<sub>III-7</sub>, and/or R<sub>III-7</sub> and R<sub>III-8</sub> are taken together and form at least one four to eight membered ring that is partially saturated or fully unsaturated optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by R<sub>III-5</sub> and R<sub>III-6</sub>, or R<sub>III-6</sub> and R<sub>III-7</sub>, and/or R<sub>III-7</sub>  
 30 and R<sub>III-8</sub> are optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro,



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cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent optionally having from one to nine fluorines;

provided that the R<sub>III-5</sub>, R<sub>III-6</sub>, R<sub>III-7</sub> and/or R<sub>III-8</sub>, as the case may be, that do not form at least one ring are each independently hydrogen, halo, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or (C<sub>1</sub>-

5 C<sub>6</sub>)alkyl, said (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally having from one to nine fluorines.

Compounds of Formula III are disclosed in commonly assigned pending U.S. Patent 6,147,089 the complete disclosure of which is herein incorporated by reference.

10 In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula III:

[2R, 4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-2,3,4,6,7,8-hexahydro-cyclopenta[g]quinoline-1-carboxylic acid ethyl ester;

15 [6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-1H-2-thia-5-aza-cyclopenta[b]naphthalene-5-carboxylic acid ethylester;

[6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-2H-furo[2,3-g]quinoline-5-carboxylic acid ethyl ester;

20 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,8-tetrahydro-2H-furo[3,4-g]quinoline-1-carboxylic acid ethyl ester;

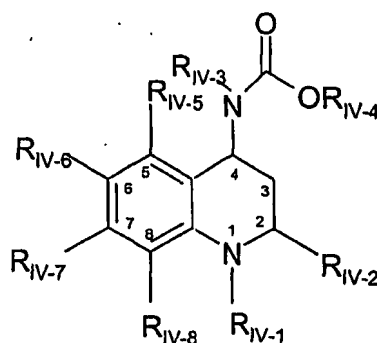
25 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,7,8,9-hexahydro-2H-benzo[g]quinoline-1-carboxylic acid propyl ester;

[7R,9S] 9-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methyl-1,2,3,7,8,9-hexahydro-6-aza-cyclopenta[a]naphthalene-6-carboxylic acid ethyl ester; and

30 [6S,8R] 6-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-methyl-1,2,3,6,7,8-hexahydro-9-aza-cyclopenta[a]naphthalene-9-carboxylic acid ethyl ester.

35 Another class of CETP inhibitors that finds utility with the present invention consists of 4-carboxyamino-2-substituted-1,2,3,4,-tetrahydroquinolines, having the Formula IV

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Formula IV

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said

5 compounds;

wherein  $R_{IV-1}$  is hydrogen,  $Y_{IV}$ ,  $W_{IV}-X_{IV}$  or  $W_{IV}-Y_{IV}$ ;

wherein  $W_{IV}$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

$X_{IV}$  is  $-O-Y_{IV}$ ,  $-S-Y_{IV}$ ,  $-N(H)-Y_{IV}$  or  $-N-(Y_{IV})_2$ ;

wherein  $Y_{IV}$  for each occurrence is independently  $Z_{IV}$  or a fully saturated,

10 partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is  
15 optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $Z_{IV}$ ;

wherein  $Z_{IV}$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently  
20 from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $Z_{IV}$  substituent is optionally mono-, di- or tri-substituted

25 independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino,

nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

- R<sub>IV-2</sub> is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo; or said R<sub>IV-2</sub> is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein said R<sub>IV-2</sub> ring is optionally attached through (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- wherein said R<sub>IV-2</sub> ring is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, oxo or (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl;

with the proviso that R<sub>IV-2</sub> is not methyl;

R<sub>IV-3</sub> is hydrogen or Q<sub>IV</sub>;

- wherein Q<sub>IV</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>IV</sub>;

wherein V<sub>IV</sub> is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken

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independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $V_{IV}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituents are also optionally substituted with from one to nine fluorines;

$R_{IV-4}$  is  $Q_{IV-1}$  or  $V_{IV-1}$ ;

wherein  $Q_{IV-1}$  a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{IV-1}$ ;

wherein  $V_{IV-1}$  is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said  $V_{IV-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein either  $R_{IV-3}$  must contain  $V_{IV}$  or  $R_{IV-4}$  must contain  $V_{IV-1}$ ;

$R_{IV-5}$ ,  $R_{IV-6}$ ,  $R_{IV-7}$  and  $R_{IV-8}$  are each independently hydrogen, a bond, nitro or halo wherein said bond is substituted with  $T_{IV}$  or a partially saturated, fully saturated or fully unsaturated  $(C_1-C_{12})$  straight or branched carbon chain wherein carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur

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and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and  
 5 said carbon is optionally mono-substituted with T<sub>IV</sub>;

wherein T<sub>IV</sub> is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken  
 10 independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said T<sub>IV</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-  
 15 N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines; and

20 wherein R<sub>IV-5</sub> and R<sub>IV-6</sub>, or R<sub>IV-6</sub> and R<sub>IV-7</sub>, and/or R<sub>IV-7</sub> and R<sub>IV-8</sub> may also be taken together and can form at least one four to eight membered ring that is partially saturated or fully unsaturated optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by R<sub>IV-5</sub> and R<sub>IV-6</sub>, or R<sub>IV-6</sub> and R<sub>IV-7</sub>, and/or  
 25 R<sub>IV-7</sub> and R<sub>IV-8</sub> are optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro,  
 30 cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

with the proviso that when R<sub>IV-2</sub> is carboxyl or (C<sub>1</sub>-C<sub>4</sub>)alkylcarboxyl, then R<sub>IV-1</sub> is not hydrogen.

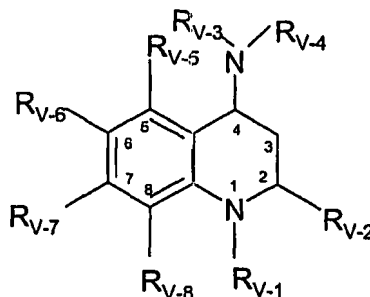
Compounds of Formula IV are disclosed in commonly assigned pending U.S. Patent 6,197,786 the complete disclosure of which is herein incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula IV:

- 5 [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-chloro-2-cyclopropyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 10 [2S,4S] 2-cyclopropyl-4-[(3,5-dichloro-benzyl)-methoxycarbonyl-amino]-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
- 15 [2R,4R] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 20 [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclobutyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 25 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methoxymethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 30 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxy-ethyl ester;
- 35 [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- 40 [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester; and
- 45 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester.

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Another class of CETP inhibitors that finds utility with the present invention consists of 4-amino substituted-2-substituted-1,2,3,4,-tetrahydroquinolines, having the Formula V



5

Formula V

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

10 wherein  $R_{V-1}$  is  $Y_V$ ,  $W_V-X_V$  or  $W_V-Y_V$ ;

wherein  $W_V$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

$X_V$  is  $-O-Y_V$ ,  $-S-Y_V$ ,  $-N(H)-Y_V$  or  $-N-(Y_V)_2$ ;

wherein  $Y_V$  for each occurrence is independently  $Z_V$  or a fully saturated,  
partially unsaturated or fully unsaturated one to ten membered straight or branched  
15 carbon chain wherein the carbons, other than the connecting carbon, may optionally  
be replaced with one or two heteroatoms selected independently from oxygen, sulfur  
and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently  
with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is  
optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted  
20 with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon  
chain is optionally mono-substituted with  $Z_V$ ;

wherein  $Z_V$  is a partially saturated, fully saturated or fully unsaturated three to  
eight membered ring optionally having one to four heteroatoms selected independently  
from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially  
25 saturated, fully saturated or fully unsaturated three to six membered rings, taken  
independently, optionally having one to four heteroatoms selected independently from  
nitrogen, sulfur and oxygen;

wherein said  $Z_V$  substituent is optionally mono-, di- or tri-substituted  
independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-$

C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

R<sub>V-2</sub> is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo; or said R<sub>V-2</sub> is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein said R<sub>V-2</sub> ring is optionally attached through (C<sub>1</sub>-C<sub>4</sub>)alkyl;

wherein said R<sub>V-2</sub> ring is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, oxo or (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl;

R<sub>V-3</sub> is hydrogen or Q<sub>V</sub>;  
 wherein Q<sub>V</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>V</sub>;

wherein V<sub>V</sub> is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently



from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

- 5            wherein said  $V_V$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally  
 10   mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituents are also optionally substituted with from one to nine fluorines;

$R_{V-4}$  is cyano, formyl,  $W_{V-1}Q_{V-1}$ ,  $W_{V-1}V_{V-1}$ ,  $(C_1-C_4)$ alkylene $V_{V-1}$  or  $V_{V-2}$ ;

- 15            wherein  $W_{V-1}$  is carbonyl, thiocarbonyl, SO or  $SO_2$ ,  
               wherein  $Q_{V-1}$  a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is  
 20   optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{V-1}$ ;

- wherein  $V_{V-1}$  is a partially saturated, fully saturated or fully unsaturated three to  
 25   six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

- 30            wherein said  $V_{V-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, hydroxy, oxo, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

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wherein  $V_{V-2}$  is a partially saturated, fully saturated or fully unsaturated five to seven membered ring containing one to four heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said  $V_{V-2}$  substituent is optionally mono-, di- or tri-substituted  
5 independently with halo,  $(C_1-C_2)$ alkyl,  $(C_1-C_2)$ alkoxy, hydroxy, or oxo wherein said  $(C_1-C_2)$ alkyl optionally has from one to five fluorines; and

wherein  $R_{V-4}$  does not include oxycarbonyl linked directly to the  $C^4$  nitrogen;

wherein either  $R_{V-3}$  must contain  $V_V$  or  $R_{V-4}$  must contain  $V_{V-1}$ ;

$R_{V-5}$ ,  $R_{V-6}$ ,  $R_{V-7}$  and  $R_{V-8}$  are independently hydrogen, a bond, nitro or halo  
10 wherein said bond is substituted with  $T_V$  or a partially saturated, fully saturated or fully unsaturated  $(C_1-C_{12})$  straight or branched carbon chain wherein carbon may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said  
15 carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $T_V$ ;

wherein  $T_V$  is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected  
20 independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $T_V$  substituent is optionally mono-, di- or tri-substituted  
25 independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino,  
30 said  $(C_1-C_6)$ alkyl substituent also optionally has from one to nine fluorines;

wherein  $R_{V-5}$  and  $R_{V-6}$ , or  $R_{V-6}$  and  $R_{V-7}$ , and/or  $R_{V-7}$  and  $R_{V-8}$  may also be taken together and can form at least one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

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wherein said rings formed by  $R_{V,5}$  and  $R_{V,6}$ , or  $R_{V,6}$  and  $R_{V,7}$ , and/or  $R_{V,7}$  and  $R_{V,8}$  are optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_8)$ alkyl,  $(C_1-C_4)$ alkylsulfonyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_8)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_8)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_8)$ alkylamino wherein said  $(C_1-C_8)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_8)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_8)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_8)$ alkylamino, said  $(C_1-C_8)$ alkyl substituent also optionally has from one to nine fluorines.

Compounds of Formula V are disclosed in commonly assigned pending U.S. Patent 6,140,343 the complete disclosure of which is herein incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula V:

- 15 [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- 20 [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 25 [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
- 30 [2S,4S] 4-[1-(3,5-bis-trifluoromethyl-benzyl)-ureido]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- 35 [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methoxymethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- 40 [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- 45 [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

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[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

5 [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

10

[2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

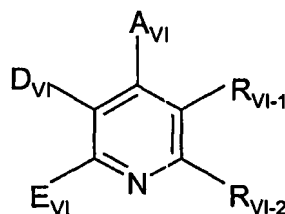
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[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester; and

[2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

20

Another class of CETP inhibitors that finds utility with the present invention consists of cycloalkano-pyridines having the Formula VI



Formula VI

25 and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

in which

$A_{VI}$  denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with up to five identical or different substituents in the form of a halogen, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy or a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy containing up to 7 carbon atoms each, or in the form of a group according to the formula  $-BNR_{VI-3}R_{VI-4}$ , wherein

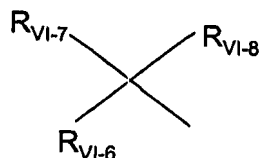
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$R_{VI-3}$  and  $R_{VI-4}$  are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms,

35

$D_{VI}$  denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with a phenyl, nitro, halogen, trifluoromethyl or trifluoromethoxy, or a radical according to the formula  $R_{VI-5}-L_{VI-1}$ .

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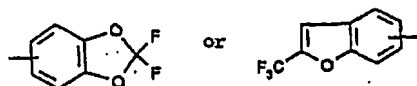
or  $R_{VI-9}-T_{VI}-V_{VI}-X_{VI}$ , wherein

- 5  $R_{VI-5}$ ,  $R_{VI-8}$  and  $R_{VI-9}$  denote, independently from one another, a cycloalkyl containing 3 to 6 carbon atoms, or an aryl containing 6 to 10 carbon atom or a 5- to 7-membered, optionally benzo-condensed, saturated or unsaturated, mono-, bi- or tricyclic heterocycle containing up to 4 heteroatoms from the series of S, N and/or O, wherein the rings are optionally substituted, in the case of the nitrogen-containing rings also via the N function, with up to five identical or different substituents in the form of a halogen, trifluoromethyl, nitro, hydroxyl, cyano, carboxyl, trifluoromethoxy, a straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl containing up to 6 carbon atoms each, an aryl or trifluoromethyl-substituted aryl containing 6 to 10 carbon atoms each, or an optionally benzo-condensed, aromatic 5- to 7-membered heterocycle containing up to 3 heteroatoms from the series of S, N and/or O, and/or in the form of a group according to the formula  $BOR_{VI-10}$ ,  $-SR_{VI-11}$ ,  $-SO_2R_{VI-12}$  or  $BNR_{VI-13}R_{VI-14}$ , wherein

- $R_{VI-10}$ ,  $R_{VI-11}$  and  $R_{VI-12}$  denote, independently from one another, an aryl containing 6 to 10 carbon atoms, which is in turn substituted with up to two identical or different substituents in the form of a phenyl, halogen or a straight-chain or branched alkyl containing up to 6 carbon atoms,

$R_{VI-13}$  and  $R_{VI-14}$  are identical or different and have the meaning of  $R_{VI-3}$  and  $R_{VI-4}$  given above, or

$R_{VI-5}$  and/or  $R_{VI-8}$  denote a radical according to the formula

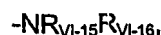


25

$R_{VI-7}$  denotes a hydrogen or halogen, and

$R_{VI-8}$  denotes a hydrogen, halogen, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, a straight-chain or branched alkoxy or alkyl containing up to 6 carbon atoms each, or a radical according to the formula

30



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wherein

$R_{VI-15}$  and  $R_{VI-16}$  are identical or different and have the meaning of  $R_{VI-3}$  and  $R_{VI-4}$  given above, or

$R_{VI-7}$  and  $R_{VI-8}$  together form a radical according to the formula  $=O$  or  $=NR_{VI-17}$ ,

5 wherein

$R_{VI-17}$  denotes a hydrogen or a straight-chain or branched alkyl, alkoxy or acyl containing up to 6 carbon atoms each,

$L_{VI}$  denotes a straight-chain or branched alkylene or alkenylene chain containing up to 8 carbon atoms each, which are optionally substituted with up to two  
10 hydroxyl groups,

$T_{VI}$  and  $X_{VI}$  are identical or different and denote a straight-chain or branched alkylene chain containing up to 8 carbon atoms, or

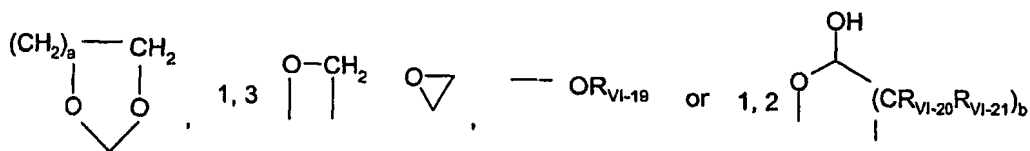
$T_{VI}$  or  $X_{VI}$  denotes a bond,

$V_{VI}$  denotes an oxygen or sulfur atom or an  $BNR_{VI-18}$  group, wherein

15  $R_{VI-18}$  denotes a hydrogen or a straight-chain or branched alkyl containing up to 6 carbon atoms or a phenyl,

$E_{VI}$  denotes a cycloalkyl containing 3 to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally substituted with a cycloalkyl containing 3 to 8 carbon atoms or a hydroxyl, or a phenyl, which is optionally  
20 substituted with a halogen or trifluoromethyl,

$R_{VI-1}$  and  $R_{VI-2}$  together form a straight-chain or branched alkylene chain containing up to 7 carbon atoms, which must be substituted with a carbonyl group and/or a radical according to the formula



25 wherein

$a$  and  $b$  are identical or different and denote a number equaling 1, 2 or 3,

$R_{VI-19}$  denotes a hydrogen atom, a cycloalkyl containing 3 to 7 carbon atoms, a straight-chain or branched silylalkyl containing up to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally  
30 substituted with a hydroxyl, a straight-chain or a branched alkoxy containing up to 6 carbon atoms or a phenyl, which may in turn be substituted with a halogen, nitro,

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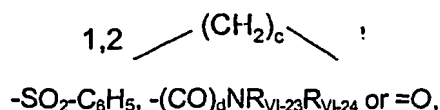
trifluoromethyl, trifluoromethoxy or phenyl or tetrazole-substituted phenyl, and an alkyl that is optionally substituted with a group according to the formula  $\text{BOR}_{\text{VI-22}}$ , wherein

$\text{R}_{\text{VI-22}}$  denotes a straight-chain or branched acyl containing up to 4 carbon atoms or benzyl, or

- 5  $\text{R}_{\text{VI-19}}$  denotes a straight-chain or branched acyl containing up to 20 carbon atoms or benzoyl, which is optionally substituted with a halogen, trifluoromethyl, nitro or trifluoromethoxy, or a straight-chain or branched fluoroacyl containing up to 8 carbon atoms,

- 10  $\text{R}_{\text{VI-20}}$  and  $\text{R}_{\text{VI-21}}$  are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms, or

- 15  $\text{R}_{\text{VI-20}}$  and  $\text{R}_{\text{VI-21}}$  together form a 3- to 6-membered carbocyclic ring, and the carbocyclic rings formed are optionally substituted, optionally also geminally, with up to six identical or different substituents in the form of trifluoromethyl, hydroxyl, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy containing 3 to 7 carbon atoms each, a straight-chain or branched alkoxy carbonyl, alkoxy or alkylthio containing up to 6 carbon atoms each, or a straight-chain or branched alkyl containing up to 6 carbon atoms, which is in turn substituted with up to two identical or different substituents in the form of a hydroxyl, benzyloxy, trifluoromethyl, benzoyl, a straight-chain or branched alkoxy, oxyacyl or carboxyl containing up to 4 carbon atoms each and/or a phenyl, which may in turn be substituted with a halogen, trifluoromethyl or trifluoromethoxy, and/or the carbocyclic rings formed are optionally substituted, also geminally, with up to five identical or different substituents in the form of a phenyl, benzoyl, thiophenyl or sulfonylbenzyl, which in turn are optionally substituted with a halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or optionally in the form of a radical according to the formula



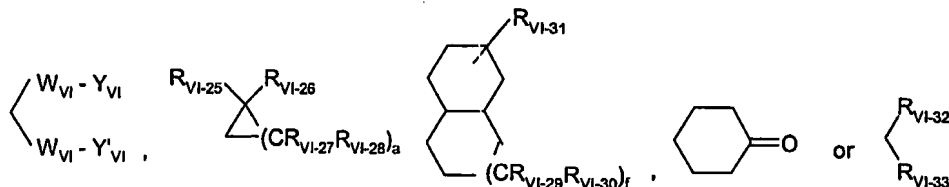
wherein

- 30 c is a number equaling 1, 2, 3 or 4,  
d is a number equaling 0 or 1,

$\text{R}_{\text{VI-23}}$  and  $\text{R}_{\text{VI-24}}$  are identical or different and denote a hydrogen, cycloalkyl containing 3 to 6 carbon atoms, a straight-chain or branched alkyl containing up to 6 carbon atoms, benzyl or phenyl, which is optionally substituted with up to two identical or different substituents in the form of halogen, trifluoromethyl, cyano, phenyl or nitro,

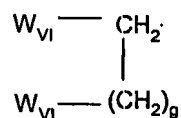
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and/or the carbocyclic rings formed are optionally substituted with a spiro-linked radical according to the formula



wherein

- 5  $W_{VI}$  denotes either an oxygen atom or a sulfur atom,  
 $Y_{VI}$  and  $Y=_{VI}$  together form a 2- to 6-membered straight-chain or branched alkylene chain,  
 $e$  is a number equaling 1, 2, 3, 4, 5, 6 or 7,  
 $f$  is a number equaling 1 or 2,
- 10  $R_{VI-25}$ ,  $R_{VI-26}$ ,  $R_{VI-27}$ ,  $R_{VI-28}$ ,  $R_{VI-29}$ ,  $R_{VI-30}$  and  $R_{VI-31}$  are identical or different and denote a hydrogen, trifluoromethyl, phenyl, halogen or a straight-chain or branched alkyl or alkoxy containing up to 6 carbon atoms each, or  
 $R_{VI-25}$  and  $R_{VI-26}$  or  $R_{VI-27}$  and  $R_{VI-28}$  each together denote a straight-chain or branched alkyl chain containing up to 6 carbon atoms or
- 15  $R_{VI-25}$  and  $R_{VI-26}$  or  $R_{VI-27}$  and  $R_{VI-28}$  each together form a radical according to the formula



wherein

- $W_{VI}$  has the meaning given above,
- 20  $g$  is a number equaling 1, 2, 3, 4, 5, 6 or 7,  
 $R_{VI-32}$  and  $R_{VI-33}$  together form a 3- to 7-membered heterocycle, which contains an oxygen or sulfur atom or a group according to the formula  $SO$ ,  $SO_2$  or  $BNR_{VI-34}$ ,  
wherein  
 $R_{VI-34}$  denotes a hydrogen atom, a phenyl, benzyl, or a straight-chain or
- 25 branched alkyl containing up to 4 carbon atoms, and salts and N oxides thereof, with the exception of 5(6H)-quinolones, 3-benzoyl-7,8-dihydro-2,7,7-trimethyl-4-phenyl.
- Compounds of Formula VI are disclosed in European Patent Application No. EP 818448 A1, U.S. Patent 6,207,671 and U.S. Patent 6,064,148 the complete disclosures of which are herein incorporated by reference.



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In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula VI:

2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-3-(4-trifluoromethylbenzoyl)-4,6,7,8-tetrahydro-1H-quinolin-5-one;

5

2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-3-(4-trifluoromethylbenzoyl)-7,8-dihydro-6H-quinolin-5-one;

10

[2-cyclopentyl-4-(4-fluorophenyl)-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanone;

[5-(t-butyldimethylsilyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanone;

15

[5-(t-butyldimethylsilyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanol;

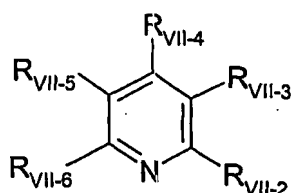
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5-(t-butyldimethylsilyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-3-[fluoro-(4-trifluoromethylphenyl)-methyl]-7,7-dimethyl-5,6,7,8-tetrahydroquinoline;

2-cyclopentyl-4-(4-fluorophenyl)-3-[fluoro-(4-trifluoromethylphenyl)-methyl]-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-5-ol.

Another class of CETP inhibitors that finds utility with the present invention consists of substituted-pyridines having the Formula VII

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Formula VII

or a pharmaceutically acceptable salt or tautomer thereof,

30 wherein

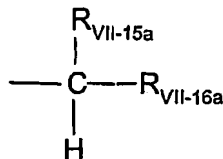
$R_{VII-2}$  and  $R_{VII-6}$  are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of  $R_{VII-2}$  and  $R_{VII-6}$  is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

35

$R_{VII-3}$  is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl  
-CHO,

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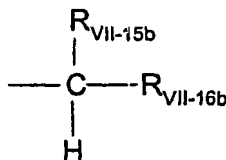
-CO<sub>2</sub>R<sub>VII-7</sub>, wherein R<sub>VII-7</sub> is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



- wherein R<sub>VII-15a</sub> is selected from the group consisting of hydroxy, hydrogen,
- 5 halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy, and
- R<sub>VII-16a</sub> is selected from the group consisting of alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heteroaryl, and heterocyclyl, arylalkoxy, trialkylsilyloxy;
- 10 R<sub>VII-4</sub> is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy,
- 15 heterocyclyloxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloxyloxy, heteroaryoxyloxy, heterocyclyloxyloxy, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, heterocyclyloxy carbonyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
- 20 heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkylamino, alkenylamino, alkynylamino, arylamino, heteroarylamino, heterocyclylamino, arylalkylamino, diarylamino, diheteroarylamino, alkylaryl amino, alkylheteroaryl amino, arylheteroaryl amino, trialkylsilyl, trialkenylsilyl, triarylsilyl,
- 25 -CO(O)N(R<sub>VII-8a</sub>R<sub>VII-8b</sub>), wherein R<sub>VII-8a</sub> and R<sub>VII-8b</sub> are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, -SO<sub>2</sub>R<sub>VII-9</sub>, wherein R<sub>VII-9</sub> is selected from the group consisting of hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, -OP(O)(OR<sub>VII-10a</sub>)(OR<sub>VII-10b</sub>), wherein R<sub>VII-10a</sub> and R<sub>VII-10b</sub> are independently selected from the group consisting of hydrogen, hydroxy, alkyl,
- 30 alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and -OP(S)(OR<sub>VII-11a</sub>)(OR<sub>VII-11b</sub>), wherein R<sub>VII-11a</sub> and R<sub>VII-11b</sub> are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

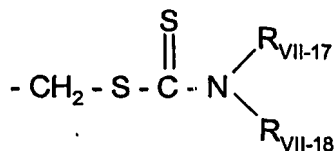
-45-

- $R_{VII-5}$  is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocyclyloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl, alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl, heterocyclyloxyalkenyl, cyano, hydroxymethyl,  $-CO_2R_{VII-14}$ , wherein  $R_{VII-14}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

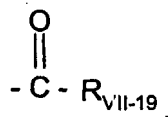


- wherein  $R_{VII-15b}$  is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryloxy, and alkylsulfonyloxy, and

$R_{VII-16b}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;



- wherein  $R_{VII-17}$  and  $R_{VII-18}$  are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



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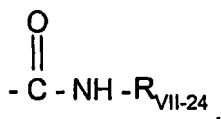
wherein  $R_{VII-19}$  is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl,  $-SR_{VII-20}$ ,  $-OR_{VII-21}$ , and  $BR_{VII-22}CO_2R_{VII-23}$ , wherein

$R_{VII-20}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroarylamino, arylheteroarylamino,

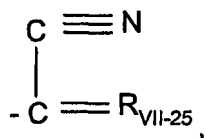
$R_{VII-21}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl,

$R_{VII-22}$  is selected from the group consisting of alkylene or arylene, and

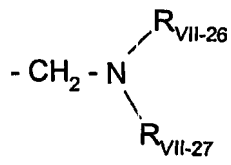
$R_{VII-23}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



wherein  $R_{VII-24}$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, aralkenyl, and aralkynyl;

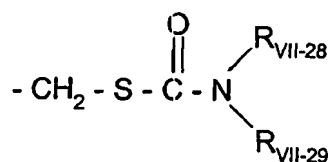
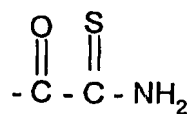
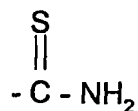


wherein  $R_{VII-25}$  is heterocyclidenyl;

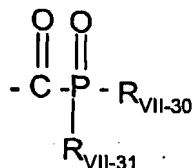


wherein  $R_{VII-26}$  and  $R_{VII-27}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

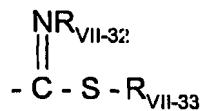
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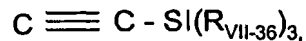
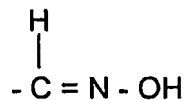
wherein  $\text{R}_{\text{VII-28}}$  and  $\text{R}_{\text{VII-29}}$  are independently selected from the group consisting  
 5 of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



wherein  $\text{R}_{\text{VII-30}}$  and  $\text{R}_{\text{VII-31}}$  are independently alkoxy, alkenoxy, alkynoxy, aryloxy,  
 heteroaryloxy, and heterocyclyloxy; and

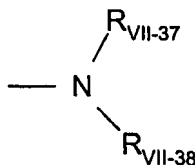


10 wherein  $\text{R}_{\text{VII-32}}$  and  $\text{R}_{\text{VII-33}}$  are independently selected from the group consisting  
 of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

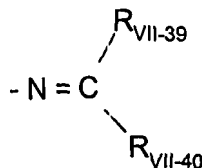


wherein  $\text{R}_{\text{VII-36}}$  is selected from the group consisting of alkyl, alkenyl, aryl,  
 heteroaryl and heterocyclyl;

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wherein  $\text{R}_{\text{VII-37}}$  and  $\text{R}_{\text{VII-38}}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

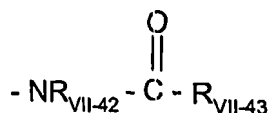


- 5        wherein  $\text{R}_{\text{VII-39}}$  is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio, and

- 10         $\text{R}_{\text{VII-40}}$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxy, heterocyclylalkenoxy, heterocyclylalkynoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio;

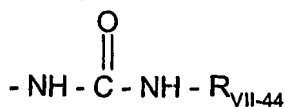


wherein  $\text{R}_{\text{VII-41}}$  is heterocyclidenyl;

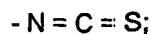
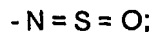


- 15        wherein  $\text{R}_{\text{VII-42}}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, and

$\text{R}_{\text{VII-43}}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, and haloheterocyclyl;



- 20        wherein  $\text{R}_{\text{VII-44}}$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



- 25         $\text{--- N} = \text{C} = \text{O};$

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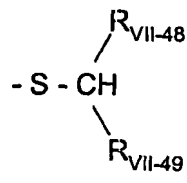
- N<sub>3</sub>;- SR<sub>VII-45</sub>

wherein R<sub>VII-45</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclalkenyl, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclthioalkenyl, aminocarbonylalkyl, aminocarbonylalkenyl, aminocarbonylalkynyl, aminocarbonylaryl, aminocarbonylheteroaryl, and aminocarbonylheterocyclyl,

-SR<sub>VII-46</sub>, and -CH<sub>2</sub>R<sub>VII-47</sub>,

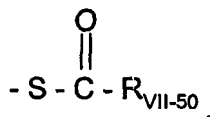
wherein R<sub>VII-46</sub> is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

R<sub>VII-47</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl; and



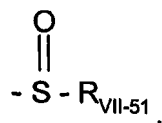
wherein R<sub>VII-48</sub> is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

R<sub>VII-49</sub> is selected from the group consisting of alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl;

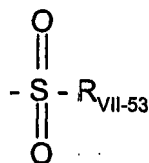


wherein R<sub>VII-50</sub> is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy;

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wherein  $\text{R}_{\text{VII-51}}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and



5

wherein  $\text{R}_{\text{VII-53}}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

provided that when  $\text{R}_{\text{VII-5}}$  is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the corresponding heterocyclylalkyl or heterocyclylalkenyl is other than  $\delta$ -lactone; and

10

provided that when  $\text{R}_{\text{VII-4}}$  is aryl, heteroaryl or heterocyclyl, and one of  $\text{R}_{\text{VII-2}}$  and  $\text{R}_{\text{VII-6}}$  is trifluoromethyl, then the other of  $\text{R}_{\text{VII-2}}$  and  $\text{R}_{\text{VII-6}}$  is difluoromethyl.

Compounds of Formula VII are disclosed in WO 9941237-A1, the complete disclosure of which is incorporated by reference.

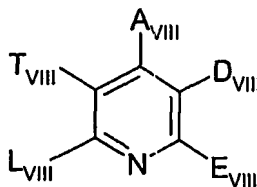
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In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula VII:

Dimethyl 5,5-dithiobis[2-difluoromethyl-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate].

20

Another class of CETP inhibitors that finds utility with the present invention consists of substituted pyridines having the Formula VIII



Formula VIII

or a pharmaceutically acceptable salt, enantiomers, or stereoisomers thereof, in which



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A<sub>VIII</sub> stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula

5 -NR<sub>VIII-1</sub>R<sub>VIII-2</sub>, wherein

R<sub>VIII-1</sub> and R<sub>VIII-2</sub> are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 6 carbon atoms,

D<sub>VIII</sub> stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,

10 E<sub>VIII</sub> and L<sub>VIII</sub> are either identical or different and stand for straight-chain or branched alkyl with up to 8 carbon atoms, which is optionally substituted by cycloalkyl with 3 to 8 carbon atoms, or stands for cycloalkyl with 3 to 8 carbon atoms, or

E<sub>VIII</sub> has the above-mentioned meaning and

15 L<sub>VIII</sub> in this case stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula

-NR<sub>VIII-3</sub>R<sub>VIII-4</sub>, wherein

20 R<sub>VIII-3</sub> and R<sub>VIII-4</sub> are identical or different and have the meaning given above for R<sub>VIII-1</sub> and R<sub>VIII-2</sub>, or

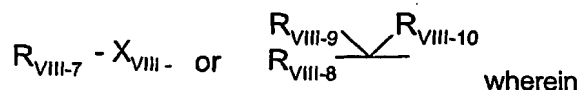
E<sub>VIII</sub> stands for straight-chain or branched alkyl with up to 8 carbon atoms, or stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula

-NR<sub>VIII-5</sub>R<sub>VIII-6</sub>, wherein

R<sub>VIII-5</sub> and R<sub>VIII-6</sub> are identical or different and have the meaning given above for R<sub>VIII-1</sub> and R<sub>VIII-2</sub>, and

30 L<sub>VIII</sub> in this case stands for straight-chain or branched alkoxy with up to 8 carbon atoms or for cycloalkoxy with 3 to 8 carbon atoms,

T<sub>VIII</sub> stands for a radical of the formula



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$R_{VIII-7}$  and  $R_{VIII-8}$  are identical or different and denote cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms, or denote a 5- to 7-member aromatic, optionally benzo-condensed, heterocyclic compound with up to 3 heteroatoms from the series S, N and/or O, which are optionally substituted up to 3 times in an identical  
 5 manner or differently by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, by straight-chain or branched alkyl, acyl, alkoxy, or alkoxycarbonyl with up to 6 carbon atoms each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by halogen, trifluoromethyl, or trifluoromethoxy, and/or the rings are substituted by a group of the formula

10  $-NR_{VIII-11}R_{VIII-12}$ , wherein

$R_{VIII-11}$  and  $R_{VIII-12}$  are identical or different and have the meaning given above for  $R_{VIII-1}$  and  $R_{VIII-2}$ ,

$X_{VIII}$  denotes a straight or branched alkyl chain or alkenyl chain with 2 to 10 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

15  $R_{VIII-9}$  denotes hydrogen, and

$R_{VIII-10}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, mercapto, trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula

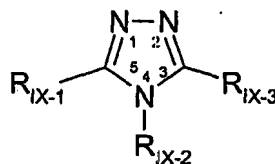
$-NR_{VIII-13}R_{VIII-14}$ , wherein

20  $R_{VIII-13}$  and  $R_{VIII-14}$  are identical or different and have the meaning given above for  $R_{VIII-1}$  and  $R_{VIII-2}$ , or

$R_{VIII-9}$  and  $R_{VIII-10}$  form a carbonyl group together with the carbon atom.

Compounds of Formula VIII are disclosed in WO 9804528, the complete disclosure of which is incorporated by reference.

25 Another class of CETP inhibitors that finds utility with the present invention consists of substituted 1,2,4-triazoles having the Formula IX



Formula IX

or a pharmaceutically acceptable salt or tautomer thereof;

30 wherein  $R_{IX-1}$  is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

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wherein  $R_{IX-2}$  is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl,  
wherein

$R_{IX-2}$  is optionally substituted at a substitutable position with one or more radicals  
independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl,  
5 alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino  
and dialkylamino; and

wherein  $R_{IX-3}$  is selected from hydrido, -SH and halo;  
provided  $R_{IX-2}$  cannot be phenyl or 4-methylphenyl when  $R_{IX-1}$  is higher alkyl and when  
 $R_{IX-3}$  is BSH.

10 Compounds of Formula IX are disclosed in WO 9914204, the complete  
disclosure of which is incorporated by reference.

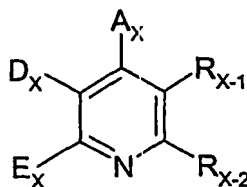
In a preferred embodiment, the CETP inhibitor is selected from the  
following compounds of Formula IX:

- 15 2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(2-fluorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(2-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
20 2,4-dihydro-4-(3-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(2-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(3-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
25 4-cyclohexyl-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(3-pyridyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
30 2,4-dihydro-4-(2-ethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(2,6-dimethylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-4-(4-phenoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
35 4-(1,3-benzodioxol-5-yl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
4-(2-chlorophenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
40 2,4-dihydro-4-(4-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-5-tridecyl-4-(3-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;  
2,4-dihydro-5-tridecyl-4-(3-fluorophenyl)-3H-1,2,4-triazole-3-thione;  
45

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- 4-(3-chloro-4-methylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(2-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 5 4-(4-benzyloxyphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(2-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 10 2,4-dihydro-5-tridecyl-4-(4-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(1-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(3-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 15 2,4-dihydro-4-(4-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(3,4-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(2,5-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 20 2,4-dihydro-4-(2-methoxy-5-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 4-(4-aminosulfonylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;  
 25 2,4-dihydro-5-dodecyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(3-methoxyphenyl)-5-tetradecyl-3H-1,2,4-triazole-3-thione;  
 2,4-dihydro-4-(3-methoxyphenyl)-5-undecyl-3H-1,2,4-triazole-3-thione; and  
 30 2,4-dihydro-(4-methoxyphenyl)-5-pentadecyl-3H-1,2,4-triazole-3-thione.

Another class of CETP inhibitors that finds utility with the present invention consists of hetero-tetrahydroquinolines having the Formula X



Formula X

and pharmaceutically acceptable salts, enantiomers, or stereoisomers or N-oxides of said compounds;

in which

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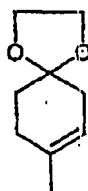
- $A_x$  represents cycloalkyl with 3 to 8 carbon atoms or a 5 to 7-membered, saturated, partially saturated or unsaturated, optionally benzo-condensed heterocyclic ring containing up to 3 heteroatoms from the series comprising S, N and/or O, that in case of a saturated heterocyclic ring is bonded to a nitrogen function, optionally
- 5 bridged over it, and in which the aromatic systems mentioned above are optionally substituted up to 5-times in an identical or different substituents in the form of halogen, nitro, hydroxy, trifluoromethyl, trifluoromethoxy or by a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy each having up to 7 carbon atoms or by a group of the formula  $BNR_{X-3}R_{X-4}$ ,
- 10 in which

$R_{X-3}$  and  $R_{X-4}$  are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

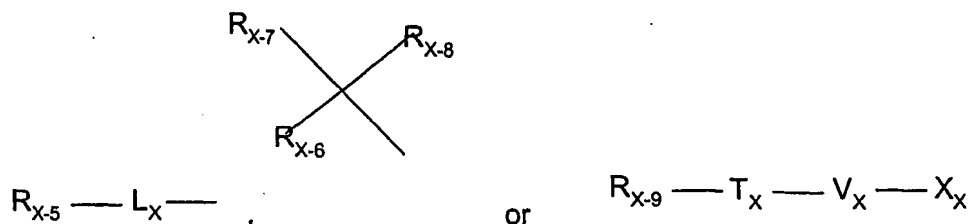
or

15

$A_x$  represents a radical of the formula



- $D_x$  represents an aryl having 6 to 10 carbon atoms, that is optionally
- 20 substituted by phenyl, nitro, halogen, trifluoromethyl or trifluoromethoxy, or it represents a radical of the formula



in which

- $R_{X-5}$ ,  $R_{X-6}$  and  $R_{X-9}$  independently of one another denote cycloalkyl having 3 to 6
- 25 carbon atoms, or an aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-condensed saturated or unsaturated, mono-, bi-, or tricyclic

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heterocyclic ring from the series consisting of S, N and/or O, in which the rings are substituted, optionally, in case of the nitrogen containing aromatic rings via the N function, with up to 5 identical or different substituents in the form of halogen, trifluoromethyl, nitro, hydroxy, cyano, carbonyl, trifluoromethoxy, straight straight-chain  
 5 or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy, or alkoxycarbonyl each having up to 6 carbon atoms, by aryl or trifluoromethyl-substituted aryl each having 6 to 10 carbon atoms or by an, optionally benzo-condensed, aromatic 5- to 7-membered heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N, and/or O, and/or substituted by a group of the formula  $\text{BOR}_{X-10}$ ,  $-\text{SR}_{X-11}$ ,  $\text{SO}_2\text{R}_{X-12}$  or  $\text{BNR}_{X-13}$ ,

10  $^{13}\text{R}_{X-14}$ ,

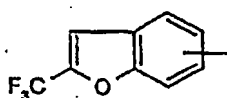
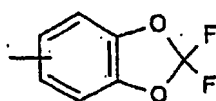
in which

$\text{R}_{X-10}$ ,  $\text{R}_{X-11}$  and  $\text{R}_{X-12}$  independently from each other denote aryl having 6 to 10 carbon atoms, which is in turn substituted with up to 2 identical or different substituents in the form of phenyl, halogen or a straight-chain or branched alkyl having up to 6  
 15 carbon atoms,

$\text{R}_{X-13}$  and  $\text{R}_{X-14}$  are identical or different and have the meaning of  $\text{R}_{X-3}$  and  $\text{R}_{X-4}$  indicated above,

or

$\text{R}_{X-5}$  and/or  $\text{R}_{X-6}$  denote a radical of the formula



20

or

$\text{R}_{X-7}$  denotes hydrogen or halogen, and

$\text{R}_{X-8}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl having up to 6 carbon  
 25 atoms or a radical of the formula

$\text{BNR}_{X-15}\text{R}_{X-16}$ ,

in which

$\text{R}_{X-15}$  and  $\text{R}_{X-16}$  are identical or different and have the meaning of  $\text{R}_{X-3}$  and  $\text{R}_{X-4}$  indicated above,

30 or

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$R_{X-7}$  and  $R_{X-8}$  together form a radical of the formula  $=O$  or  $=NR_{X-17}$ ,

in which

$R_{X-17}$  denotes hydrogen or straight chain or branched alkyl, alkoxy or acyl having up to 6 carbon atoms,

5  $L_X$  denotes a straight chain or branched alkylene or alkenylene chain having up to 8 carbon atoms, that are optionally substituted with up to 2 hydroxy groups,

$T_X$  and  $X_X$  are identical or different and denote a straight chain or branched alkylene chain with up to 8 carbon atoms

or

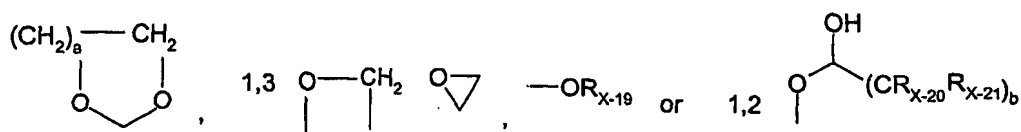
10  $T_X$  or  $X_X$  denotes a bond,

$V_X$  represents an oxygen or sulfur atom or an  $BNR_{X-18}$ -group, in which

$R_{X-18}$  denotes hydrogen or straight chain or branched alkyl with up to 6 carbon atoms or phenyl,

15  $E_X$  represents cycloalkyl with 3 to 8 carbon atoms, or straight chain or branched alkyl with up to 8 carbon atoms, that is optionally substituted by cycloalkyl with 3 to 8 carbon atoms or hydroxy, or represents a phenyl, that is optionally substituted by halogen or trifluoromethyl,

20  $R_{X-1}$  and  $R_{X-2}$  together form a straight-chain or branched alkylene chain with up to 7 carbon atoms, that must be substituted by carbonyl group and/or by a radical with the formula



in which a and b are identical or different and denote a number equaling 1,2, or 3,

25  $R_{X-19}$  denotes hydrogen, cycloalkyl with 3 up to 7 carbon atoms, straight chain or branched silylalkyl with up to 8 carbon atoms or straight chain or branched alkyl with up to 8 carbon atoms, that are optionally substituted by hydroxyl, straight chain or branched alkoxy with up to 6 carbon atoms or by phenyl, which in turn might be substituted by halogen, nitro, trifluoromethyl, trifluoromethoxy or by phenyl or by tetrazole-substituted phenyl, and alkyl, optionally be substituted by a group with the formula  $BOR_{X-22}$ ,

30 in which

$R_{X-22}$  denotes a straight chain or branched acyl with up to 4 carbon atoms or benzyl,

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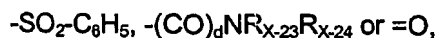
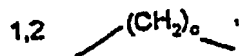
or

$R_{X-19}$  denotes straight chain or branched acyl with up to 20 carbon atoms or benzoyl, that is optionally substituted by halogen, trifluoromethyl, nitro or trifluoromethoxy, or it denotes straight chain or branched fluoroacyl with up to 8 carbon atoms and 9 fluorine atoms,

$R_{X-20}$  and  $R_{X-21}$  are identical or different and denote hydrogen, phenyl or straight chain or branched alkyl with up to 6 carbon atoms,

or

$R_{X-20}$  and  $R_{X-21}$  together form a 3- to 6- membered carbocyclic ring, and the carbocyclic rings formed are optionally substituted, optionally also geminally, with up to six identical or different substituents in the form of trifluoromethyl, hydroxy, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy with 3 to 7 carbon atoms each, by straight chain or branched alkoxy carbonyl, alkoxy or alkylthio with up to 6 carbon atoms each or by straight chain or branched alkyl with up to 6 carbon atoms, which in turn is substituted with up to 2 identically or differently by hydroxyl, benzyloxy, trifluoromethyl, benzoyl, straight chain or branched alkoxy, oxyacyl or carbonyl with up to 4 carbon atoms each and/or phenyl, which may in turn be substituted with a halogen, trifluoromethyl or trifluoromethoxy, and/or the formed carbocyclic rings are optionally substituted, also geminally, with up to 5 identical or different substituents in the form of phenyl, benzoyl, thiophenyl or sulfonylbenzyl, which in turn are optionally substituted by halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or optionally are substituted by a radical with the formula



in which

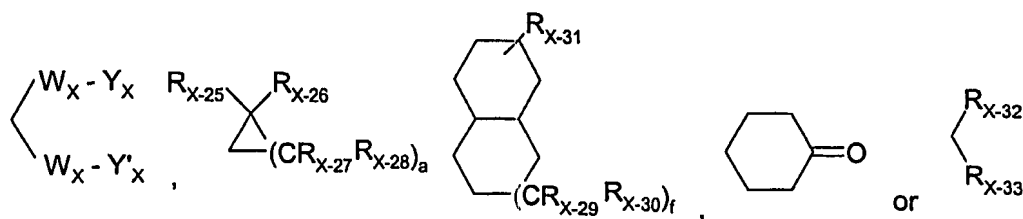
c denotes a number equaling 1, 2, 3, or 4,

d denotes a number equaling 0 or 1,

$R_{X-23}$  and  $R_{X-24}$  are identical or different and denote hydrogen, cycloalkyl with 3 to 6 carbon atoms, straight chain or branched alkyl with up to 6 carbon atoms, benzyl or phenyl, that is optionally substituted with up to 2 identically or differently by halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the formed carbocyclic rings are substituted optionally by a spiro-linked radical with the formula



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in which

$W_X$  denotes either an oxygen or a sulfur atom

- 5  $Y_X$  and  $Y'_X$  together form a 2 to 6 membered straight chain or branched alkylene chain,

$e$  denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

$f$  denotes a number equaling 1 or 2,

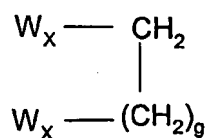
- $R_{X-25}$ ,  $R_{X-26}$ ,  $R_{X-27}$ ,  $R_{X-28}$ ,  $R_{X-29}$ ,  $R_{X-30}$  and  $R_{X-31}$  are identical or different and  
 10 denote hydrogen, trifluoromethyl, phenyl, halogen or straight chain or branched alkyl or alkoxy with up to 6 carbon atoms each,

or

$R_{X-25}$  and  $R_{X-26}$  or  $R_{X-27}$  and  $R_{X-28}$  respectively form together a straight chain or branched alkyl chain with up to 6 carbon atoms,

- 15 or

$R_{X-25}$  and  $R_{X-26}$  or  $R_{X-27}$  and  $R_{X-28}$  each together form a radical with the formula



in which

$W_X$  has the meaning given above,

- 20  $g$  denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

$R_{X-32}$  and  $R_{X-33}$  form together a 3- to 7- membered heterocycle, which contains an oxygen or sulfur atom or a group with the formula  $\text{SO}$ ,  $\text{SO}_2$  or

$-\text{NR}_{X-34}$ ,

in which

- 25  $R_{X-34}$  denotes hydrogen, phenyl, benzyl or straight or branched alkyl with up to 4 carbon atoms.

Compounds of Formula X are disclosed in WO 9914215, the complete disclosure of which is incorporated by reference.

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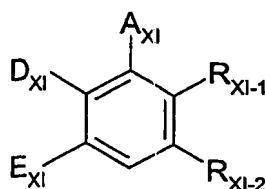
In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula X:

2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(4-trifluoromethylbenzoyl)-5,6,7,8-tetrahydroquinoline;

2-cyclopentyl-3-[fluoro-(4-trifluoromethylphenyl)methyl]-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-5,6,7,8-tetrahydroquinoline; and

2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(trifluoromethylbenzyl)-5,6,7,8-tetrahydroquinoline.

Another class of CETP inhibitors that finds utility with the present invention consists of substituted tetrahydro naphthalines and analogous compound having the Formula XI



Formula XI

and stereoisomers, stereoisomer mixtures, and salts thereof, in which

A<sub>XI</sub> stands for cycloalkyl with 3 to 8 carbon atoms, or stands for aryl with 6 to 10 carbon atoms, or stands for a 5- to 7-membered, saturated, partially unsaturated or unsaturated, possibly benzocondensated, heterocycle with up to 4 heteroatoms from the series S, N and/or O, where aryl and the heterocyclic ring systems mentioned above are substituted up to 5-fold, identical or different, by cyano, halogen, nitro, carboxyl, hydroxy, trifluoromethyl, trifluoro- methoxy, or by straight-chain or branched alkyl, acyl, hydroxyalkyl, alkylthio, alkoxycarbonyl, oxyalkoxycarbonyl or alkoxy each with up to 7 carbon atoms, or by a group of the formula

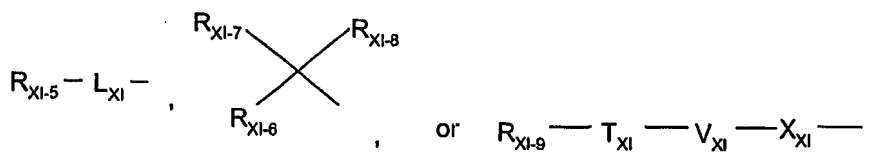
-NR<sub>XI-3</sub>R<sub>XI-4</sub>,

in which

R<sub>XI-3</sub> and R<sub>XI-4</sub> are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 6 carbon atoms

D<sub>XI</sub> stands for a radical of the formula

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in which

- $R_{X1-5}$ ,  $R_{X1-8}$  and  $R_{X1-9}$ , independent of each other, denote cycloalkyl with 3 to 6 carbon atoms, or denote aryl with 6 to 10 carbon atoms, or denote a 5- to 7-membered, possibly benzocondensated, saturated or unsaturated, mono-, bi- or tricyclic heterocycle with up to 4 heteroatoms of the series S, N and/or O, where the cycles are possibly substituted in the case of the nitrogen-containing rings also via the N-function up to 5-fold, identical or different, by halogen, trifluoromethyl, nitro, hydroxy, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl with up to 6 carbon atoms each. by aryl or trifluoromethyl substituted aryl with 6 to 10 carbon atoms each, or by a possibly benzocondensated aromatic 5- to 7-membered heterocycle with up to 3 heteroatoms of the series S, N and/or O, and/or are substituted by a group of the formula  $-OR_{X1-10}$ ,  $-SR_{X1-11}$ ,  $-SO_2R_{X1-12}$  or  $-NR_{X1-13}R_{X1-14}$ ,

in which

$R_{X1-10}$ ,  $R_{X1-11}$  and  $R_{X1-12}$ , independent of each other, denote aryl with 6 to 10 carbon atoms, which itself is substituted up to 2-fold, identical or different, by phenyl, halogen. or by straight-chain or branched alkyl with up to 6 carbon atoms,

$R_{X1-13}$  and  $R_{X1-14}$  are identical or different and have the meaning given above for

$R_{X1-3}$  and  $R_{X1-4}$ ,

or

$R_{X1-5}$  and/or  $R_{X1-6}$  denote a radical of the formula



$R_{X1-7}$  denotes hydrogen, halogen or methyl,

and

$R_{X1-8}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl with up to 6 carbon atoms each, or a radical of the formula  $-NR_{X1-15}R_{X1-16}$ ,

in which



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by phenyl or tetrazol, and alkyl is possibly substituted by a group of the formula  $-OR_{X1}$ .

22,

in which

$R_{X1-22}$  denotes straight-chain or branched acyl with up to 4 carbon atoms, or

5 benzyl,

or

$R_{X1-19}$  denotes straight-chain or branched acyl with up to 20 carbon atoms or benzoyl, which is possibly substituted by halogen, trifluoromethyl, nitro or trifluoromethoxy, or denotes straight-chain or branched fluoroacyl with up to 8 carbon atoms and 9 fluorine atoms,

10

$R_{X1-20}$  and  $R_{X1-21}$  are identical or different, denoting hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

or

$R_{X1-20}$  and  $R_{X1-21}$  together form a 3- to 6-membered carbocycle, and, possibly also geminally, the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$ , is possibly substituted up to 6-fold, identical or different, by trifluoromethyl, hydroxy, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy with 3 to 7 carbon atoms each, by straight-chain or branched alkoxycarbonyl, alkoxy or alkoxythio with up to 6 carbon atoms each, or by straight-chain or branched alkyl with up to 6 carbon atoms, which itself is substituted up to 2-fold,

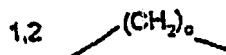
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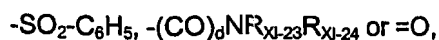
identical or different, by hydroxyl, benzyloxy, trifluoromethyl, benzoyl, straight-chain or branched alkoxy, oxyacyl or carboxyl with up to 4 carbon atoms each, and/or phenyl- which itself can be substituted by halogen, trifluoromethyl or trifluoromethoxy, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is substituted, also geminally,

25

possibly up to 5-fold, identical or different, by phenyl, benzoyl, thiophenyl or sulfbenzyl -which themselves are possibly substituted by halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is possibly substituted by a radical of the formula



30



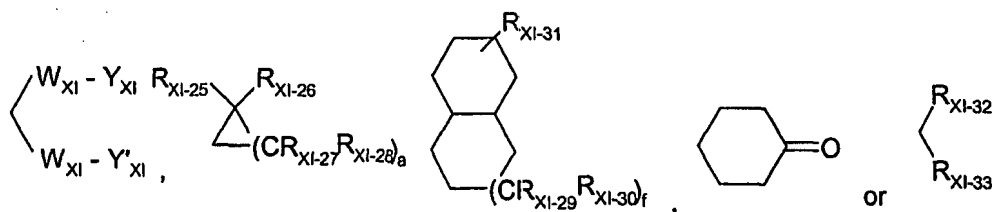
in which

c denotes a number 1, 2, 3 or 4,

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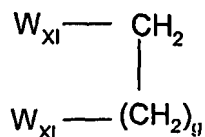
d denotes a number 0 or 1,

- $R_{X1-23}$  and  $R_{X1-24}$  are identical or different and denote hydrogen, cycloalkyl with 3 to 6 carbon atoms, straight-chain or branched alkyl with up to 6 carbon atoms, benzyl or phenyl, which is possibly substituted up to 2-fold, identical or different, by halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is possibly substituted by a spiro-jointed radical of the formula



in which

- $W_{X1}$  denotes either an oxygen or a sulfur atom,
- $Y_{X1}$  and  $Y'_{X1}$  together form a 2- to 6-membered straight-chain or branched alkylene chain,
- e is a number 1, 2, 3, 4, 5, 6 or 7,
- f denotes a number 1 or 2,
- $R_{X1-25}$ ,  $R_{X1-26}$ ,  $R_{X1-27}$ ,  $R_{X1-28}$ ,  $R_{X1-29}$ ,  $R_{X1-30}$  and  $R_{X1-31}$  are identical or different and denote hydrogen, trifluoromethyl, phenyl, halogen, or straight-chain or branched alkyl or alkoxy with up to 6 carbon atoms each,
- or
- $R_{X1-25}$  and  $R_{X1-26}$  or  $R_{X1-27}$  and  $R_{X1-28}$  together form a straight-chain or branched alkyl chain with up to 6 carbon atoms,
- or
- $R_{X1-25}$  and  $R_{X1-26}$  or  $R_{X1-27}$  and  $R_{X1-28}$  together form a radical of the formula



in which

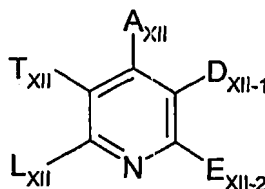
- $W_{X1}$  has the meaning given above,
- g is a number 1, 2, 3, 4, 5, 6 or 7,
- $R_{X1-32}$  and  $R_{X1-33}$  together form a 3- to 7-membered heterocycle that contains an oxygen- or sulfur atom or a group of the formula SO, SO<sub>2</sub> or -NR<sub>X1-34</sub>,
- in which

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$R_{XI-34}$  denotes hydrogen, phenyl, benzyl, or straight-chain or branched alkyl with up to 4 carbon atoms.

Compounds of Formula XI are disclosed in WO 9914174, the complete disclosure of which is incorporated by reference.

- 5 Another class of CETP inhibitors that finds utility with the present invention consists of 2-aryl-substituted pyridines having the Formula (XII)



Formula XII

- 10 or pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds,  
in which

- 15  $A_{XII}$  and  $E_{XII}$  are identical or different and stand for aryl with 6 to 10 carbon atoms which is possibly substituted, up to 5-fold identical or different, by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, nitro or by straight-chain or branched alkyl, acyl, hydroxy alkyl or alkoxy with up to 7 carbon atoms each, or by a group of the formula  $-NR_{XII-1}R_{XII-2}$ ,

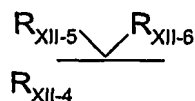
where

- $R_{XII-1}$  and  $R_{XII-2}$  are identical or different and are meant to be hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

- 20  $D_{XII}$  stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,

$L_{XII}$  stands for cycloalkyl with 3 to 8 carbon atoms or for straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms, or by hydroxy,

- 25  $T_{XII}$  stands for a radical of the formula  $R_{XII-3}-X_{XII}$  or



where

$R_{XII-3}$  and  $R_{XII-4}$  are identical or different and are meant to be cycloalkyl with 3 to

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8 carbon atoms, or aryl with 6 to 10 carbon atoms, or a 5- to 7-membered aromatic, possibly benzocondensated heterocycle with up to 3 heteroatoms from the series S, N and/or O, which are possibly substituted. up to 3-fold identical or different, by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, nitro, by straight-chain or  
5 branched alkyl, acyl, alkoxy or alkoxycarbonyl with up to 6 carbon atoms each. or by phenyl, phenoxy or phenylthio which in turn can be substituted by halogen. trifluoromethyl or trifluoromethoxy, and/or where the cycles are possibly substituted by a group of the formula  $-NR_{XII-7}R_{XII-8}$ ,

where

10  $R_{XII-7}$  and  $R_{XII-8}$  are identical or different and have the meaning of  $R_{XII-1}$  and  $R_{XII-2}$  given above,

$X_{XII}$  is a straight-chain or branched alkyl or alkenyl with 2 to 10 carbon atoms each, possibly substituted up to 2-fold by hydroxy or halogen,

$R_{XII-5}$  stands for hydrogen,

15 and

$R_{XII-6}$  means to be hydrogen, halogen, mercapto, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula  $BNR_{XII-9}R_{XII-10}$ ,

where

20  $R_{XII-9}$  and  $R_{XII-10}$  are identical or different and have the meaning of  $R_{XII-1}$  and  $R_{XII-2}$  given above,

or

$R_{XII-5}$  and  $R_{XII-6}$ , together with the carbon atom, form a carbonyl group.

Compounds of Formula XII are disclosed in EP 796846-A1, U.S. Patent  
25 6,127,383 and U.S. Patent 5,925,645 the complete disclosures of which are incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XII:

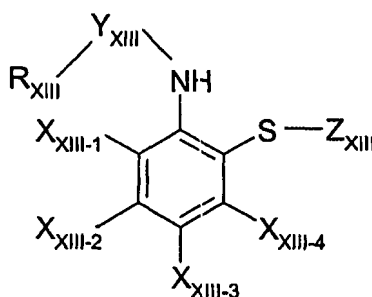
- 30 4,6-bis-(p-fluorophenyl)-2-isopropyl-3-[(p-trifluoromethylphenyl)-(fluoro)-methyl]-5-(1-hydroxyethyl)pyridine;  
2,4-bis-(4-fluorophenyl)-6-isopropyl-5-[4-(trifluoromethylphenyl)-fluoromethyl]-3-hydroxymethyl)pyridine; and  
35 2,4-bis-(4-fluorophenyl)-6-isopropyl-5-[2-(3-trifluoromethylphenyl)vinyl]-3-hydroxymethyl)pyridine.



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Another class of CETP inhibitors that finds utility with the present invention consists of compounds having the Formula (XIII)

5



Formula XIII

or pharmaceutically acceptable salts, enantiomers, stereoisomers, hydrates, or solvates of said compounds, in which

- 10  $R_{XIII}$  is a straight chain or branched  $C_{1-10}$  alkyl; straight chain or branched  $C_{2-10}$  alkenyl; halogenated  $C_{1-4}$  lower alkyl;  $C_{3-10}$  cycloalkyl that may be substituted;  $C_{5-8}$  cycloalkenyl that may be substituted;  $C_{3-10}$  cycloalkyl  $C_{1-10}$  alkyl that may be substituted; aryl that may be substituted; aralkyl that may be substituted; or a 5- or 6-membered heterocyclic group having 1 to 3 nitrogen atoms, oxygen atoms or sulfur
- 15 atoms that may be substituted,

$X_{XIII-1}$ ,  $X_{XIII-2}$ ,  $X_{XIII-3}$ ,  $X_{XIII-4}$  may be the same or different and are a hydrogen atom; halogen atom;  $C_{1-4}$  lower alkyl; halogenated  $C_{1-4}$  lower alkyl;  $C_{1-4}$  lower alkoxy; cyano group; nitro group; acyl; or aryl, respectively;

$Y_{XIII}$  is  $-CO-$ ; or  $BSO_2-$ ; and

- 20  $Z_{XIII}$  is a hydrogen atom; or mercapto protective group.

Compounds of Formula XIII are disclosed in WO 98/35937, the complete disclosure of which is incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XIII:

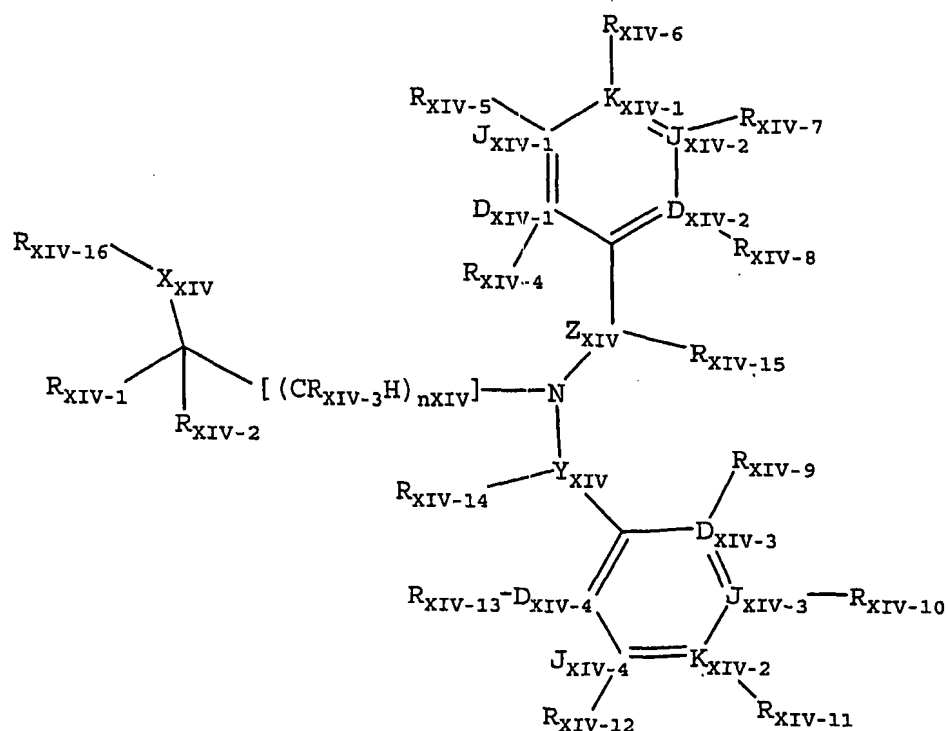
25

N,N'-(dithiodi-2,1-phenylene)bis[2,2-dimethyl-propanamide];

N,N'-(dithiodi-2,1-phenylene)bis[1-methyl-cyclohexanecarboxamide];

- N,N'-(dithiodi-2,1-phenylene)bis[1-(3-methylbutyl)-cyclopentanecarboxamide];
- 5 N,N'-(dithiodi-2,1-phenylene)bis[1-(3-methylbutyl)-cyclohexanecarboxamide];
- N,N'-(dithiodi-2,1-phenylene)bis[1-(2-ethylbutyl)-cyclohexanecarboxamide];
- N,N'-(dithiodi-2,1-phenylene)bis-tricyclo[3.3.1.<sup>3,7</sup>]decane-1-carboxamide;
- 10 propanethioic acid, 2-methyl-, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester;
- propanethioic acid, 2,2-dimethyl-, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester; and
- 15 ethanethioic acid, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester.

- Another class of CETP inhibitors that finds utility with the present invention
- 20 consists of polycyclic aryl and heteroaryl tertiary-heteroalkylamines having the Formula XIV



## Formula XIV

and pharmaceutically acceptable forms thereof, wherein:

$n_{XIV}$  is an integer selected from 0 through 5;

5  $R_{XIV-1}$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxyalkyl, and haloalkenyloxyalkyl;

$X_{XIV}$  is selected from the group consisting of O, H, F, S, S(O), NH, N(OH), N(alkyl), and N(alkoxy);

10  $R_{XIV-16}$  is selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, 15 halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, monocarboalkoxyalkyl, monocarboalkoxy, dicarboalkoxyalkyl, monocarboxamido, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, dialkoxyphosphonoalkyl, trialkylsilyl, and a spacer selected from the 20 group consisting of a covalent single bond and a linear spacer moiety having from 1 through 4 contiguous atoms linked to the point of bonding of an aromatic substituent selected from the group consisting of  $R_{XIV-4}$ ,  $R_{XIV-8}$ ,  $R_{XIV-9}$ , and  $R_{XIV-13}$  to form a heterocyclyl ring having from 5 through 10 contiguous members with the provisos that said spacer moiety is other than a covalent single bond when  $R_{XIV-2}$  is alkyl and there is 25 no  $R_{XIV-16}$  wherein X is H or F;

$D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  is a covalent bond, no more than one of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  is O, no more than one of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  is S, one of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  must be a covalent bond when two of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  are O and S, and no more than four of  $D_{XIV-1}$ ,  $D_{XIV-2}$ ,  $J_{XIV-1}$ ,  $J_{XIV-2}$  and  $K_{XIV-1}$  are N;

$D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one

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- of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  is a covalent bond, no more than one of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  is O, no more than one of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  is S, one of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  must be a covalent bond when two of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  are O and S, and no more than four of  $D_{XIV-3}$ ,  $D_{XIV-4}$ ,  $J_{XIV-3}$ ,  $J_{XIV-4}$  and  $K_{XIV-2}$  are N;

- $R_{XIV-2}$  is independently selected from the group consisting of hydrido, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aralkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, aloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, alkylsulfinylalkyl, alkylsulfonylalkyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl;

- $R_{XIV-2}$  and  $R_{XIV-3}$  are taken together to form a linear spacer moiety selected from the group consisting of a covalent single bond and a moiety having from 1 through 6 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl having from 3 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

- $R_{XIV-3}$  is selected from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, hydroxyalkyl, amino, alkylamino, dialkylamino, acyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, heteroarylthio, aralkylthio, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aroyl, heteroaroyl, aralkylthioalkyl,

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- heteroaralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy,
- 5 halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl,
- 10 cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyposphono, diaralkoxyposphono, dialkoxyposphonoalkyl, and diaralkoxyposphonoalkyl;
- 15  $Y_{XIV}$  is selected from a group consisting of a covalent single bond,  $(C(R_{XIV-14})_2)_{q_{XIV}}$  wherein  $q_{XIV}$  is an integer selected from 1 and 2 and  $(CH(R_{XIV-14}))_{g_{XIV}}-W_{XIV}-(CH(R_{XIV-14}))_{p_{XIV}}$  wherein  $g_{XIV}$  and  $p_{XIV}$  are integers independently selected from 0 and 1;
- $R_{XIV-14}$  is independently selected from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, acyl, aroyl,
- 20 heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl,
- 25 halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl,
- 30 aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl,

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carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, a spacer selected from a moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of  $R_{XIV-9}$  and  $R_{XIV-13}$  to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members and a spacer selected from a moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of  $R_{XIV-4}$  and  $R_{XIV-8}$  to form a heterocyclyl having from 5 through 8 contiguous members with the proviso that, when  $Y_{XIV}$  is a covalent bond, an  $R_{XIV-14}$  substituent is not attached to  $Y_{XIV}$ ;

$R_{XIV-14}$  and  $R_{XIV-14}$ , when bonded to the different atoms, are taken together to form a group selected from the group consisting of a covalent bond, alkylene, haloalkylene, and a spacer selected from a group consisting of a moiety having a chain length of 2 to 5 atoms connected to form a ring selected from the group of a saturated cycloalkyl having from 5 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

$R_{XIV-14}$  and  $R_{XIV-14}$ , when bonded to the same atom are taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the group consisting of a cycloalkyl having from 4 through 8 contiguous members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

$W_{XIV}$  is selected from the group consisting of O, C(O), C(S), C(O)N( $R_{XIV-14}$ ), C(S)N( $R_{XIV-14}$ ), ( $R_{XIV-14}$ )NC(O), ( $R_{XIV-14}$ )NC(S), S, S(O), S(O)<sub>2</sub>, S(O)<sub>2</sub>N( $R_{XIV-14}$ ), ( $R_{XIV-14}$ )NS(O)<sub>2</sub>, and N( $R_{XIV-14}$ ) with the proviso that  $R_{XIV-14}$  is selected from other than halo and cyano;

$Z_{XIV}$  is independently selected from a group consisting of a covalent single bond,  $(C(R_{XIV-15})_2)_{q_{XIV-2}}$  wherein  $q_{XIV-2}$  is an integer selected from 1 and 2,  $(CH(R_{XIV-15}))_{j_{XIV}}-W-(CH(R_{XIV-15}))_{k_{XIV}}$  wherein  $j_{XIV}$  and  $k_{XIV}$  are integers independently selected from 0 and 1 with the proviso that, when  $Z_{XIV}$  is a covalent single bond, an  $R_{XIV-15}$  substituent is not attached to  $Z_{XIV}$ ;

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- $R_{XIV-15}$  is independently selected, when  $Z_{XIV}$  is  $(C(R_{XIV-15})_2)_{q_{XIV}}$  wherein  $q_{XIV}$  is an integer selected from 1 and 2, from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, a spacer selected from a moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of  $R_{XIV-4}$  and  $R_{XIV-8}$  to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer selected from a moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of  $R_{XIV-9}$  and  $R_{XIV-13}$  to form a heterocyclyl having from 5 through 8 contiguous members;

$R_{XIV-15}$  and  $R_{XIV-15}$ , when bonded to the different atoms, are taken together to form a group selected from the group consisting of a covalent bond, alkylene, haloalkylene, and a spacer selected from a group consisting of a moiety having a chain length of 2 to 5 atoms connected to form a ring selected from the group of a

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saturated cycloalkyl having from 5 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

5  $R_{XIV-15}$  and  $R_{XIV-15}$ , when bonded to the same atom are taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the group consisting of a cycloalkyl having from 4 through 8 contiguous members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous  
10 members;

$R_{XIV-15}$  is independently selected, when  $Z_{XIV}$  is  $(CH(R_{XIV-15}))_{j_{XIV}}-W-(CH(R_{XIV-15}))_{k_{XIV}}$  wherein  $j_{XIV}$  and  $k_{XIV}$  are integers independently selected from 0 and 1, from the group consisting of hydrido, halo, cyano, aryloxy, carboxyl, acyl, aroyl, heteroaroyl, hydroxyalkyl, heteroaryloxyalkyl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfonylalkyl, alkylsulfinylalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyposphonoalkyl, diaralkoxyposphonoalkyl, a spacer selected from a linear moiety having a chain length of 3 to 6 atoms  
25 connected to the point of bonding selected from the group consisting of  $R_{XIV-4}$  and  $R_{XIV-8}$  to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer  
30



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selected from a linear moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of  $R_{XIV-8}$  and  $R_{XIV-13}$  to form a heterocyclyl ring having from 5 through 8 contiguous members;

- $R_{XIV-4}$ ,  $R_{XIV-5}$ ,  $R_{XIV-6}$ ,  $R_{XIV-7}$ ,  $R_{XIV-8}$ ,  $R_{XIV-9}$ ,  $R_{XIV-10}$ ,  $R_{XIV-11}$ ,  $R_{XIV-12}$ , and  $R_{XIV-13}$  are
- 5 independently selected from the group consisting of perhaloaryloxy, alkanoylalkyl, alkanoylalkoxy, alkanoyloxy, N-aryl-N-alkylamino, heterocyclylalkoxy, heterocyclylthio, hydroxyalkoxy, carboxamidoalkoxy, alkoxycarbonylalkoxy, alkoxycarbonylalkenyloxy, aralkanoylalkoxy, aralkenoyl, N-alkylcarboxamido, N-haloalkylcarboxamido, N-cycloalkylcarboxamido, N-arylcarboxamidoalkoxy, cycloalkylcarbonyl, cyanoalkoxy,
  - 10 heterocyclylcarbonyl, hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocycliloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-
  - 15 heteroarylamino-N-alkylamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl,
  - 20 arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido,
  - 25 diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl,
  - 30 lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido,

- alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl with the proviso that there are one to five non-hydrido ring
- 5 substituents  $R_{XIV-4}$ ,  $R_{XIV-5}$ ,  $R_{XIV-6}$ ,  $R_{XIV-7}$ , and  $R_{XIV-8}$  present, that there are one to five non-hydrido ring substituents  $R_{XIV-9}$ ,  $R_{XIV-10}$ ,  $R_{XIV-11}$ ,  $R_{XIV-12}$ , and  $R_{XIV-13}$  present, and  $R_{XIV-4}$ ,  $R_{XIV-5}$ ,  $R_{XIV-6}$ ,  $R_{XIV-7}$ ,  $R_{XIV-8}$ ,  $R_{XIV-9}$ ,  $R_{XIV-10}$ ,  $R_{XIV-11}$ ,  $R_{XIV-12}$ , and  $R_{XIV-13}$  are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- 10  $R_{XIV-4}$  and  $R_{XIV-5}$ ,  $R_{XIV-5}$  and  $R_{XIV-6}$ ,  $R_{XIV-6}$  and  $R_{XIV-7}$ ,  $R_{XIV-7}$  and  $R_{XIV-8}$ ,  $R_{XIV-8}$  and  $R_{XIV-9}$ ,  $R_{XIV-9}$  and  $R_{XIV-10}$ ,  $R_{XIV-10}$  and  $R_{XIV-11}$ ,  $R_{XIV-11}$  and  $R_{XIV-12}$ , and  $R_{XIV-12}$  and  $R_{XIV-13}$  are independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group
- 15 consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs  $R_{XIV-4}$  and  $R_{XIV-5}$ ,  $R_{XIV-5}$  and  $R_{XIV-6}$ ,  $R_{XIV-6}$  and  $R_{XIV-7}$ , and  $R_{XIV-7}$  and  $R_{XIV-8}$  are used at the same time and that no more than one
- 20 of the group consisting of spacer pairs  $R_{XIV-9}$  and  $R_{XIV-10}$ ,  $R_{XIV-10}$  and  $R_{XIV-11}$ ,  $R_{XIV-11}$  and  $R_{XIV-12}$ , and  $R_{XIV-12}$  and  $R_{XIV-13}$  are used at the same time;
- $R_{XIV-4}$  and  $R_{XIV-9}$ ,  $R_{XIV-4}$  and  $R_{XIV-13}$ ,  $R_{XIV-8}$  and  $R_{XIV-9}$ , and  $R_{XIV-8}$  and  $R_{XIV-13}$  are independently selected to form a spacer pair wherein said spacer pair is taken together to form a linear moiety wherein said linear moiety forms a ring selected from
- 25 the group consisting of a partially saturated heterocyclyl ring having from 5 through 8 contiguous members and a heteroaryl ring having from 5 through 6 contiguous members with the proviso that no more than one of the group consisting of spacer pairs  $R_{XIV-4}$  and  $R_{XIV-9}$ ,  $R_{XIV-4}$  and  $R_{XIV-13}$ ,  $R_{XIV-8}$  and  $R_{XIV-9}$ , and  $R_{XIV-8}$  and  $R_{XIV-13}$  is used at the same time.
- 30 Compounds of Formula XIV are disclosed in WO 00/18721, the entire disclosure of which is incorporated by reference.
- In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XIV:

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- 3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(3-isopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[3-(3-*t*-butylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
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- 3-[[[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(pentafluoroethyl)methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[3-(3-isopropylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3-cyclopropylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[3-(3-(2-furyl)phenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(2,3-dichlorophenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
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- 3-[[3-(4-fluorophenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(4-methylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-(3-ethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-t-butylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(3-methylphenoxy)phenyl][[3-pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(phenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-

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- (trifluoromethylthio)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[3-(pentafluoroethyl)phenyl]methyl][3-(cyclohexylmethoxy)phenyl]-amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3-isopropylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[3-(3-cyclopropylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3-(2-furyl)phenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[3-(2,3-dichlorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(4-fluorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[3-(4-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
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- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(heptafluoropropyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[3-(pentafluoroethyl)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3,5-dimethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[3-(3-ethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(3-t-butylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[3-(3-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(phenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethylthio)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[cyclohexylmethoxy]phenyl]-amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

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- 3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(heptafluoropropyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-(3-cyclopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(3-(2-furyl)phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-(4-fluorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;



- 3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(3-(N,N-dimethylamino)phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(3-difluoromethoxyphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

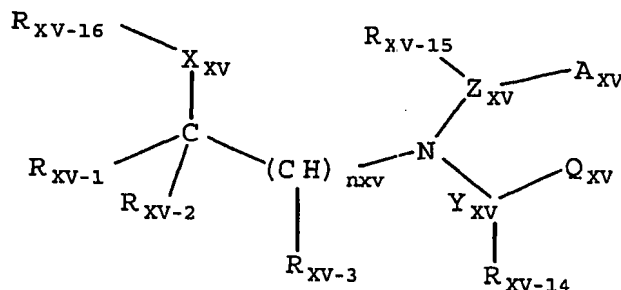
- 3-[[3-(3-cyclopropylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(3-(2-furyl)phenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(4-fluorophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-methylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[3-(5,6,7,8- tetrahydro-2-naphthoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(phenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;

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- 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[3-(3-difluoromethoxyphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol; and
- 30 3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol.

Another class of CETP inhibitors that finds utility with the present invention consists of substituted N-Aliphatic-N-Aromatic *tertiary*-Heteroalkylamines having the Formula XV

35



Formula XV

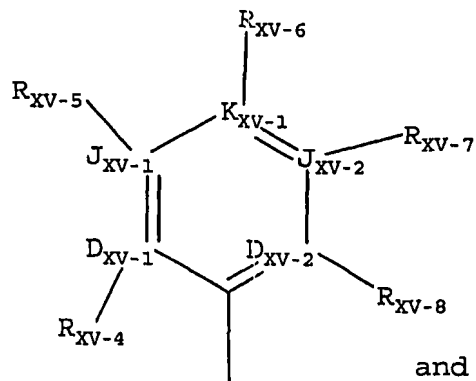
and pharmaceutically acceptable forms thereof, wherein:

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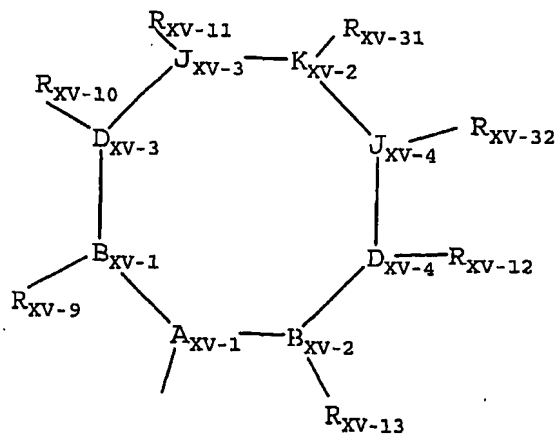
$n_{XV}$  is an integer selected from 1 through 2;

$A_{XV}$  and  $Q_{XV}$  are independently selected from the group consisting of

AQ-1

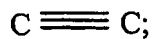


AQ-2



- 5 with the provisos that one of  $A_{XV}$  and  $Q_{XV}$  must be AQ-1 and that one of  $A_{XV}$  and  $Q_{XV}$  must be selected from the group consisting of AQ-2 and  $-\text{CH}_2(\text{CR}_{XV-37}\text{R}_{XV-38})_{vXV}-(\text{CR}_{XV-33}\text{R}_{XV-34})_{uXV}-\text{T}_{XV}-(\text{CR}_{XV-35}\text{R}_{XV-36})_{wXV}-\text{H}$ ;

$\text{T}_{XV}$  is selected from the group consisting of a single covalent bond, O, S, S(O), S(O)<sub>2</sub>, C(R<sub>XV-33</sub>)=C(R<sub>XV-35</sub>), and



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$v_{XV}$  is an integer selected from 0 through 1 with the proviso that  $v_{XV}$  is 1 when any one of  $R_{XV-33}$ ,  $R_{XV-34}$ ,  $R_{XV-35}$ , and  $R_{XV-36}$  is aryl or heteroaryl;

$u_{XV}$  and  $w_{XV}$  are integers independently selected from 0 through 6;

$A_{XV-1}$  is  $C(R_{XV-30})$ ;

- 5  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  is a covalent bond, no more than one of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  is O, no more than one of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  is S, one of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  must be a covalent bond when two of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  are O and S, and no more than four of  $D_{XV-1}$ ,  $D_{XV-2}$ ,  $J_{XV-1}$ ,  $J_{XV-2}$ , and  $K_{XV-1}$  are N;

- 15  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are independently selected from the group consisting of C,  $C(R_{XV-30})$ , N, O, S and a covalent bond with the provisos that no more than 5 of  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are a covalent bond, no more than two of  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are O, no more than two of  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are S, no more than two of  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are simultaneously O and S, and no more than two of  $B_{XV-1}$ ,  $B_{XV-2}$ ,  $D_{XV-3}$ ,  $D_{XV-4}$ ,  $J_{XV-3}$ ,  $J_{XV-4}$ , and  $K_{XV-2}$  are N;

- 20  $B_{XV-1}$  and  $D_{XV-3}$ ,  $D_{XV-3}$  and  $J_{XV-3}$ ,  $J_{XV-3}$  and  $K_{XV-2}$ ,  $K_{XV-2}$  and  $J_{XV-4}$ ,  $J_{XV-4}$  and  $D_{XV-4}$ , and  $D_{XV-4}$  and  $B_{XV-2}$  are independently selected to form an in-ring spacer pair wherein said

spacer pair is selected from the group consisting of  $C(R_{XV-33})=C(R_{XV-35})$  and  $N=N$  with the provisos that AQ-2 must be a ring of at least five contiguous members, that no more than two of the group of said spacer pairs are simultaneously

- 25  $C(R_{XV-33})=C(R_{XV-35})$  and that no more than one of the group of said spacer pairs can be  $N=N$  unless the other spacer pairs are other than  $C(R_{XV-33})=C(R_{XV-35})$ , O, N, and S;

$R_{XV-1}$  is selected from the group consisting of haloalkyl and haloalkoxymethyl;

- 30  $R_{XV-2}$  is selected from the group consisting of hydrido, aryl, alkyl, alkenyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl and heteroaryl;

$R_{XV-3}$  is selected from the group consisting of hydrido, aryl, alkyl, alkenyl, haloalkyl, and haloalkoxyalkyl;

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$Y_{XV}$  is selected from the group consisting of a covalent single bond,  $(CH_2)_q$  wherein  $q$  is an integer selected from 1 through 2 and  $(CH_2)_j-O-(CH_2)_k$  wherein  $j$  and  $k$  are integers independently selected from 0 through 1;

$Z_{XV}$  is selected from the group consisting of covalent single bond,  $(CH_2)_q$  wherein  $q$  is an integer selected from 1 through 2, and  $(CH_2)_j-O-(CH_2)_k$  wherein  $j$  and  $k$  are integers independently selected from 0 through 1;

$R_{XV-4}$ ,  $R_{XV-8}$ ,  $R_{XV-9}$  and  $R_{XV-13}$  are independently selected from the group consisting of hydrido, halo, haloalkyl, and alkyl;

$R_{XV-30}$  is selected from the group consisting of hydrido, alkoxy, alkoxyalkyl, halo, haloalkyl, alkylamino, alkylthio, alkylthioalkyl, alkyl, alkenyl, haloalkoxy, and haloalkoxyalkyl with the proviso that  $R_{XV-30}$  is selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

$R_{XV-30}$ , when bonded to  $A_{XV-1}$ , is taken together to form an intra-ring linear spacer connecting the  $A_{XV-1}$ -carbon at the point of attachment of  $R_{XV-30}$  to the point of bonding of a group selected from the group consisting of  $R_{XV-10}$ ,  $R_{XV-11}$ ,  $R_{XV-12}$ ,  $R_{XV-31}$ , and  $R_{XV-32}$  wherein said intra-ring linear spacer is selected from the group consisting of a covalent single bond and a spacer moiety having from 1 through 6 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl having from 3 through 10 contiguous members, a cycloalkenyl having from 5 through 10 contiguous members, and a heterocyclyl having from 5 through 10 contiguous members;

$R_{XV-30}$ , when bonded to  $A_{XV-1}$ , is taken together to form an intra-ring branched spacer connecting the  $A_{XV-1}$ -carbon at the point of attachment of  $R_{XV-30}$  to the points of bonding of each member of any one of substituent pairs selected from the group consisting of substituent pairs  $R_{XV-10}$  and  $R_{XV-11}$ ,  $R_{XV-10}$  and  $R_{XV-31}$ ,  $R_{XV-10}$  and  $R_{XV-32}$ ,  $R_{XV-10}$  and  $R_{XV-12}$ ,  $R_{XV-11}$  and  $R_{XV-31}$ ,  $R_{XV-11}$  and  $R_{XV-32}$ ,  $R_{XV-11}$  and  $R_{XV-12}$ ,  $R_{XV-31}$  and  $R_{XV-32}$ ,  $R_{XV-31}$  and  $R_{XV-12}$ , and  $R_{XV-32}$  and  $R_{XV-12}$  and wherein said intra-ring branched spacer is selected to form two rings selected from the group consisting of cycloalkyl having from 3 through 10 contiguous members, cycloalkenyl having from 5 through 10 contiguous members, and heterocyclyl having from 5 through 10 contiguous members;

$R_{XV-4}$ ,  $R_{XV-5}$ ,  $R_{XV-6}$ ,  $R_{XV-7}$ ,  $R_{XV-8}$ ,  $R_{XV-9}$ ,  $R_{XV-10}$ ,  $R_{XV-11}$ ,  $R_{XV-12}$ ,  $R_{XV-13}$ ,  $R_{XV-31}$ ,  $R_{XV-32}$ ,  $R_{XV-33}$ ,  $R_{XV-34}$ ,  $R_{XV-35}$ , and  $R_{XV-36}$  are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocycloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl,

- heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, alkylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl with the provisos that  $R_{XV-4}$ ,  $R_{XV-5}$ ,  $R_{XV-6}$ ,  $R_{XV-7}$ ,  $R_{XV-8}$ ,  $R_{XV-9}$ ,  $R_{XV-10}$ ,  $R_{XV-11}$ ,  $R_{XV-12}$ ,  $R_{XV-13}$ ,  $R_{XV-31}$ ,  $R_{XV-32}$ ,  $R_{XV-33}$ ,  $R_{XV-34}$ ,  $R_{XV-35}$ , and  $R_{XV-36}$  are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen, that no more than three of the  $R_{XV-33}$  and  $R_{XV-34}$  substituents are simultaneously selected from other than the group consisting of hydrido and halo, and that no more than three of the  $R_{XV-35}$

and R<sub>XV-36</sub> substituents are simultaneously selected from other than the group consisting of hydrido and halo;

R<sub>XV-9</sub>, R<sub>XV-10</sub>, R<sub>XV-11</sub>, R<sub>XV-12</sub>, R<sub>XV-13</sub>, R<sub>XV-31</sub>, and R<sub>XV-32</sub> are independently selected to be oxo with the provisos that B<sub>XV-1</sub>, B<sub>XV-2</sub>, D<sub>XV-3</sub>, D<sub>XV-4</sub>, J<sub>XV-3</sub>, J<sub>XV-4</sub>, and K<sub>XV-2</sub> are  
 5 independently selected from the group consisting of C and S, no more than two of R<sub>XV-9</sub>, R<sub>XV-10</sub>, R<sub>XV-11</sub>, R<sub>XV-12</sub>, R<sub>XV-13</sub>, R<sub>XV-31</sub>, and R<sub>XV-32</sub> are simultaneously oxo, and that R<sub>XV-9</sub>, R<sub>XV-10</sub>, R<sub>XV-11</sub>, R<sub>XV-12</sub>, R<sub>XV-13</sub>, R<sub>XV-31</sub>, and R<sub>XV-32</sub> are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

10 R<sub>XV-4</sub> and R<sub>XV-5</sub>, R<sub>XV-5</sub> and R<sub>XV-6</sub>, R<sub>XV-6</sub> and R<sub>XV-7</sub>, R<sub>XV-7</sub> and R<sub>XV-8</sub>, R<sub>XV-9</sub> and R<sub>XV-10</sub>, R<sub>XV-10</sub> and R<sub>XV-11</sub>, R<sub>XV-11</sub> and R<sub>XV-31</sub>, R<sub>XV-31</sub> and R<sub>XV-32</sub>, R<sub>XV-32</sub> and R<sub>XV-12</sub>, and R<sub>XV-12</sub> and R<sub>XV-13</sub> are independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the  
 15 group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs R<sub>XV-4</sub> and R<sub>XV-5</sub>, R<sub>XV-5</sub> and R<sub>XV-6</sub>, R<sub>XV-6</sub> and R<sub>XV-7</sub>, R<sub>XV-7</sub> and R<sub>XV-8</sub> is used at the same time and that no more than  
 20 one of the group consisting of spacer pairs R<sub>XV-9</sub> and R<sub>XV-10</sub>, R<sub>XV-10</sub> and R<sub>XV-11</sub>, R<sub>XV-11</sub> and R<sub>XV-31</sub>, R<sub>XV-31</sub> and R<sub>XV-32</sub>, R<sub>XV-32</sub> and R<sub>XV-12</sub>, and R<sub>XV-12</sub> and R<sub>XV-13</sub> are used at the same time;

R<sub>XV-9</sub> and R<sub>XV-11</sub>, R<sub>XV-9</sub> and R<sub>XV-12</sub>, R<sub>XV-9</sub> and R<sub>XV-13</sub>, R<sub>XV-9</sub> and R<sub>XV-31</sub>, R<sub>XV-9</sub> and R<sub>XV-32</sub>, R<sub>XV-10</sub> and R<sub>XV-12</sub>, R<sub>XV-10</sub> and R<sub>XV-13</sub>, R<sub>XV-10</sub> and R<sub>XV-31</sub>, R<sub>XV-10</sub> and R<sub>XV-32</sub>, R<sub>XV-11</sub> and R<sub>XV-12</sub>, R<sub>XV-11</sub> and R<sub>XV-13</sub>, R<sub>XV-11</sub> and R<sub>XV-31</sub>, R<sub>XV-11</sub> and R<sub>XV-32</sub>, R<sub>XV-12</sub> and R<sub>XV-31</sub>, R<sub>XV-13</sub> and R<sub>XV-31</sub>, and R<sub>XV-13</sub> and R<sub>XV-32</sub> are independently selected to form a spacer pair wherein said spacer pair is taken together to form a linear spacer moiety selected from the group consisting of a covalent single bond and a moiety having from 1 through 3 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl having from 3 through 8  
 25 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, a saturated heterocyclyl having from 5 through 8 contiguous members and a partially saturated heterocyclyl having from 5 through 8 contiguous members with the provisos that no more than one of said group of spacer pairs is used at the same time;  
 30



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R<sub>XV-37</sub> and R<sub>XV-38</sub> are independently selected from the group consisting of hydrido, alkoxy, alkoxyalkyl, hydroxy, amino, thio, halo, haloalkyl, alkylamino, alkylthio, alkylthioalkyl, cyano, alkyl, alkenyl, haloalkoxy, and haloalkoxyalkyl.

5                   Compounds of Formula XV are disclosed in WO 00/18723, the entire disclosure of which is incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XV:

- 10    3-[[3-(4-chloro-3-ethylphenoxy)phenyl]  
      (cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 15    3-[[3-(4-chloro-3-ethylphenoxy)phenyl]  
      (cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-chloro-3-ethylphenoxy)phenyl]  
      (cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 20    3-[[3-(4-chloro-3-ethylphenoxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-  
      1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][(3-pentafluoroethyl)  
      cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25    3-[[3-(4-chloro-3-ethylphenoxy)phenyl][(3-trifluoromethoxy)  
      cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30    3-[[3-(4-chloro-3-ethylphenoxy)phenyl][(3-(1,1,2,2-  
      tetrafluoroethoxy)cyclo-hexylmethyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxyphenoxy)phenyl]  
      (cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 35    3-[[3-(3-trifluoromethoxyphenoxy)phenyl]  
      (cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxyphenoxy)phenyl]  
      (cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 40    3-[[3-(3-trifluoromethoxyphenoxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-  
      1,1,1-trifluoro-2-propanol;
- 45    3-[[3-(3-trifluoromethoxyphenoxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-  
      1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxyphenoxy)phenyl][(3-

- trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(3-isopropylphenoxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-isopropylphenoxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(3-isopropylphenoxy)phenyl](cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-isopropylphenoxy)phenyl][(3-trifluoromethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-(3-isopropylphenoxy)phenyl][(3-pentafluoroethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-isopropylphenoxy)phenyl][(3-trifluoromethoxy) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(3-isopropylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-(2,3-dichlorophenoxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl](cyclopropylmethy)amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(2,3-dichlorophenoxy)phenyl][(3-trifluoromethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl][(3-pentafluoroethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(2,3-dichlorophenoxy)phenyl][(3-trifluoromethoxy) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(2,3-dichlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)cyclo-hexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[3-(4-fluorophenoxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-fluorophenoxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-(4-fluorophenoxy)phenny]l(cyclopropylmethyl)amino]-1,1,1-triflouro-2-propanol;
- 3-[[3-(4-fluorophenoxy)phenyl][(3-trifluoromethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50

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- 3-[[3-(4-fluorophenoxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[3-(4-fluorophenoxy)phenyl][(3-trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(4-fluorophenoxy)phenyl][(3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl](cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-(1,1,2,2-tetrafluoroethoxy)-cyclohexylmethyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[3-(3-trifluoromethylbenzyloxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethylbenzyloxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[3-(3-trifluoromethylbenzyloxy)phenyl](cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;

- 3-[[[(3-trifluoromethyl)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[(3-trifluoromethoxy)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[(3-trifluoromethyl)phenyl]methyl](4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[(3-trifluoromethoxy)phenyl]methyl](4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[(3-trifluoromethyl)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[(3-trifluoromethoxy)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[(3-trifluoromethyl)phenyl]methyl][3-(4-chloro-3-ethylphenoxy)cyclo-hexyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl][3-(4-chloro-3-ethylphenoxy)cyclo-hexyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[(3-trifluoromethoxy)phenyl]methyl][3-(4-chloro-3-ethylphenoxy)cyclo-hexyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-(4-chloro-3-ethylphenoxy)-cyclohexyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[(3-trifluoromethyl)phenyl]methyl](3-phenoxy-cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-phenoxy-cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[(3-trifluoromethyl)phenyl]methyl](3-phenoxy-cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-phenoxy-cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-phenoxy-cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;

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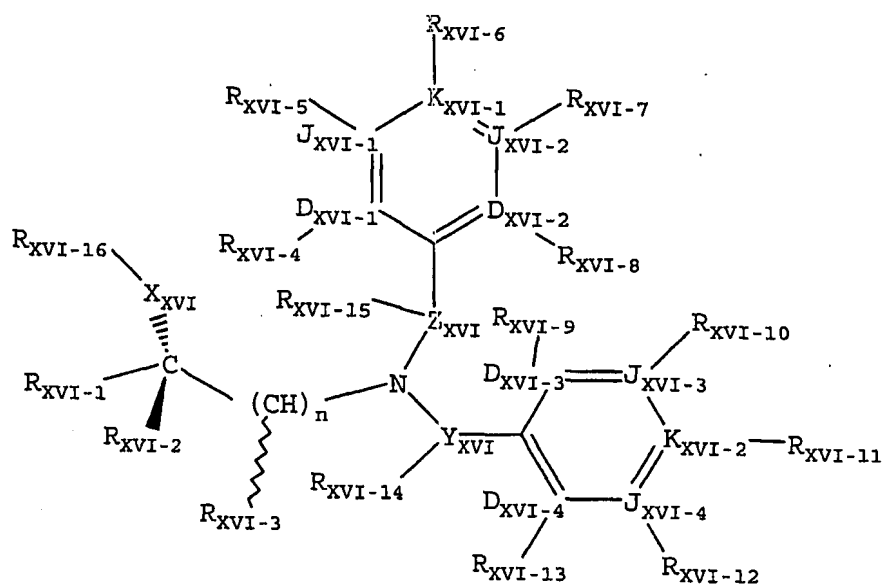
- 3-[[[(3-trifluoromethoxy)phenyl]methyl](3-phenoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[(3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3-phenoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-trifluoromethyl)phenyl]methyl](3-isopropoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-isopropoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-trifluoromethoxy)phenyl]methyl](3-isopropoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[(3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3-isopropoxy cyclohexyl)-amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[(3-trifluoromethyl)phenyl]methyl](3-cyclopentyloxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl]methyl](3-cyclopentyloxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[(3-trifluoromethoxy)phenyl]methyl](3-cyclopentyloxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[(3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3-cyclopentyloxy cyclohexyl)-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-isopropoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-cyclopentyloxy cyclohexyl)-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-phenoxy cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 40 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-trifluoromethyl cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-(4-chloro-3-ethylphenoxy) cyclo-hexyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-(1,1,2,2-tetrafluoroethoxy) cyclo-hexyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 3-[[[(2-trifluoromethyl)pyrid-6-yl]methyl](3-pentafluoroethyl cyclohexyl)-amino]-1,1,1-trifluoro-2-propanol;

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- 3-[[[(2-trifluoromethyl)pyrid-6-yl)methyl](3-trifluoromethoxycyclohexyl)-amino]-1,1,1-trifluoro-2-propanol;
- 5 3-[[[(3-trifluoromethyl)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)propyl]-amino]-1,1,1-trifluoro-2-propanol;
- 10 3-[[[(3-pentafluoroethyl)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)propyl]-amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-trifluoromethoxy)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)propyl]-amino]-1,1,1-trifluoro-2-propanol;
- 15 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)-propyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-trifluoromethyl)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)-2,2,-difluoropropyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 3-[[[(3-pentafluoroethyl)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)-2,2,-difluoropropyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-trifluoromethoxy)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)-2,2,-difluoropropyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl][3-(4-chloro-3-ethylphenoxy)-2,2,-difluoropropyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 3-[[[(3-trifluoromethyl)phenyl)methyl][3-(isopropoxy)propyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[(3-pentafluoroethyl)phenyl)methyl][3-(isopropoxy)propyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 3-[[[(3-trifluoromethoxy)phenyl)methyl][3-(isopropoxy)propyl]amino]-1,1,1-trifluoro-2-propanol;
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl][3-(isopropoxy)propyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 and
- 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl][3-(phenoxy)propyl]amino]-1,1,1-trifluoro-2-propanol.
- 45

Another class of CETP inhibitors that finds utility with the present invention consists of (R)-chiral halogenated 1-substituted amino-(n+1)-alkanols having the Formula XVI

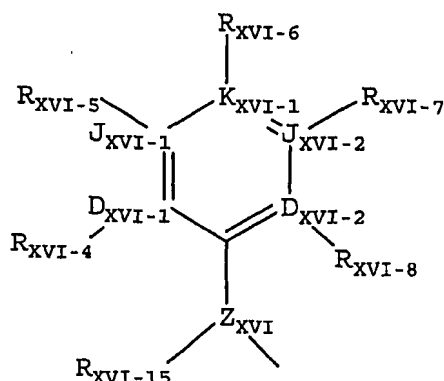
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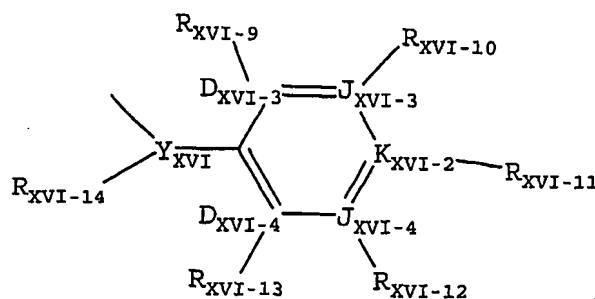
Formula XVI

- 5 and pharmaceutically acceptable forms thereof, wherein:
- $n_{XVI}$  is an integer selected from 1 through 4;
  - $X_{XVI}$  is oxy;
  - $R_{XVI-1}$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_{XVI-1}$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_{XVI-2}$  and  $(CHR_{XVI-3})_n-N(A_{XVI})Q_{XVI}$  wherein  $A_{XVI}$  is Formula XVI-(II) and  $Q$  is Formula XVI-(III);
- 10

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XVI-II



XVI-III

$R_{XVI-16}$  is selected from the group consisting of hydrido, alkyl, acyl, aroyl, heteroaroyl, trialkylsilyl, and a spacer selected from the group consisting of a covalent single bond and a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of any aromatic substituent selected from the group consisting of  $R_{XVI-4}$ ,  $R_{XVI-8}$ ,  $R_{XVI-9}$ , and  $R_{XVI-13}$  to form a heterocyclol ring having from 5 through 10 contiguous members;

$D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that no more than one of  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  is a covalent bond, no more than one  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  is be O, no more than one of  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  is S, one of  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  must be a covalent bond when two of  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  are O and S, and no more than four of  $D_{XVI-1}$ ,  $D_{XVI-2}$ ,  $J_{XVI-1}$ ,  $J_{XVI-2}$  and  $K_{XVI-1}$  is N;

$D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that no more than one is a covalent bond, no more than one of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  is O, no more than one of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  is S, no more than two of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  is O and S, one of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  must be a covalent bond when two of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  are O and S, and no more than four of  $D_{XVI-3}$ ,  $D_{XVI-4}$ ,  $J_{XVI-3}$ ,  $J_{XVI-4}$  and  $K_{XVI-2}$  are N;

$R_{XVI-2}$  is selected from the group consisting of hydrido, aryl, aralkyl, alkyl, alkenyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl,



perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, dicyanoalkyl, and carboalkoxycyanoalkyl, with the proviso that  $R_{XVI-2}$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_{XVI-1}$  and  $(CHR_{XVI-3})_n-N(A_{XVI})Q_{XVI}$ ;

$R_{XVI-3}$  is selected from the group consisting of hydrido, hydroxy, cyano, aryl, aralkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, heteroaryl, alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocycanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl, with the provisos that  $(CHR_{XVI-3})_n-N(A_{XVI})Q_{XVI}$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_{XVI-1}$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_{XVI-2}$ ;

$Y_{XVI}$  is selected from a group consisting of a covalent single bond,  $(C(R_{XVI-14})_2)_q$  wherein  $q$  is an integer selected from 1 and 2 and  $(CH(R_{XVI-14}))_g-W_{XVI}-(CH(R_{XVI-14}))_p$  wherein  $g$  and  $p$  are integers independently selected from 0 and 1;

$R_{XVI-14}$  is selected from the group consisting of hydrido, hydroxy, cyano, hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocarboalkoxyalkyl, monocycanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

$Z_{XVI}$  is selected from a group consisting of a covalent single bond,  $(C(R_{XVI-15})_2)_q$ , wherein  $q$  is an integer selected from 1 and 2, and  $(CH(R_{XVI-15}))_j-W_{XVI}-(CH(R_{XVI-15}))_k$  wherein  $j$  and  $k$  are integers independently selected from 0 and 1;

$W_{XVI}$  is selected from the group consisting of O, C(O), C(S), C(O)N( $R_{XVI-14}$ ), C(S)N( $R_{XVI-14}$ ), ( $R_{XVI-14}$ )NC(O), ( $R_{XVI-14}$ )NC(S), S, S(O), S(O)<sub>2</sub>, S(O)<sub>2</sub>N( $R_{XVI-14}$ ), ( $R_{XVI-14}$ )NS(O)<sub>2</sub>, and N( $R_{XVI-14}$ ) with the proviso that  $R_{XVI-14}$  is other than cyano;

$R_{XVI-15}$  is selected, from the group consisting of hydrido, cyano, hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocarboalkoxyalkyl, monocycanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

$R_{XVI-4}$ ,  $R_{XVI-5}$ ,  $R_{XVI-6}$ ,  $R_{XVI-7}$ ,  $R_{XVI-8}$ ,  $R_{XVI-9}$ ,  $R_{XVI-10}$ ,  $R_{XVI-11}$ ,  $R_{XVI-12}$ , and  $R_{XVI-13}$  are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocycloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl,

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- cycloalkylsulfonylalkyl, heteroaryl-amino, N-heteroaryl-amino-N-alkyl-amino, heteroaralkyl, heteroaryl-aminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy,
- 5 halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkyl-amino, alkylthio, alkylthioalkyl, aryl-amino, aralkyl-amino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroaryl-sulfinylalkyl, heteroaryl-sulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido,
- 10 alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl, amidosulfonyl, monoaryl-amidosulfonyl, arylsulfonamido, diaryl-amidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroaryl-sulfinyl, heteroaryl-sulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl,
- 15 alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially
- 20 saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and
- 25 diaralkoxyphosphonoalkyl with the proviso that  $R_{XVI-4}$ ,  $R_{XVI-5}$ ,  $R_{XVI-6}$ ,  $R_{XVI-7}$ ,  $R_{XVI-8}$ ,  $R_{XVI-9}$ ,  $R_{XVI-10}$ ,  $R_{XVI-11}$ ,  $R_{XVI-12}$ , and  $R_{XVI-13}$  are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- $R_{XVI-4}$  and  $R_{XVI-5}$ ,  $R_{XVI-5}$  and  $R_{XVI-6}$ ,  $R_{XVI-6}$  and  $R_{XVI-7}$ ,  $R_{XVI-7}$  and  $R_{XVI-8}$ ,  $R_{XVI-8}$  and  $R_{XVI-9}$ ,  $R_{XVI-9}$  and  $R_{XVI-10}$ ,  $R_{XVI-10}$  and  $R_{XVI-11}$ ,  $R_{XVI-11}$  and  $R_{XVI-12}$ , and  $R_{XVI-12}$  and  $R_{XVI-13}$  are independently
- 30 selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated

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heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs  $R_{XVI-4}$  and  $R_{XVI-5}$ ,  $R_{XVI-5}$  and  $R_{XVI-6}$ ,  $R_{XVI-6}$  and  $R_{XVI-7}$ , and  $R_{XVI-7}$  and  $R_{XVI-8}$  is used at the same time and that no more than one of the group

5 consisting of spacer pairs  $R_{XVI-9}$  and  $R_{XVI-10}$ ,  $R_{XVI-10}$  and  $R_{XVI-11}$ ,  $R_{XVI-11}$  and  $R_{XVI-12}$ , and  $R_{XVI-12}$  and  $R_{XVI-13}$  can be used at the same time;

$R_{XVI-4}$  and  $R_{XVI-9}$ ,  $R_{XVI-4}$  and  $R_{XVI-13}$ ,  $R_{XVI-8}$  and  $R_{XVI-9}$ , and  $R_{XVI-8}$  and  $R_{XVI-13}$  is independently selected to form a spacer pair wherein said spacer pair is taken together to form a linear moiety wherein said linear moiety forms a ring selected from

10 the group consisting of a partially saturated heterocyclyl ring having from 5 through 8 contiguous members and a heteroaryl ring having from 5 through 6 contiguous members with the proviso that no more than one of the group consisting of spacer pairs  $R_{XVI-4}$  and  $R_{XVI-9}$ ,  $R_{XVI-4}$  and  $R_{XVI-13}$ ,  $R_{XVI-8}$  and  $R_{XVI-9}$ , and  $R_{XVI-8}$  and  $R_{XVI-13}$  is used at the same time.

15 Compounds of Formula XVI are disclosed in WO 00/18724, the entire disclosure of which is incorporated by reference.

In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XVI:

20 (2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;

(2R)-3-[[3-(3-isopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

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(2R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

30 (2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

(2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

35 (2R)-3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

(2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

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(2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

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- (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-(3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-t-butylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[3-(3-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethylthio)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[cyclohexylmethoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-isopropylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[3-(4-fluorophenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[3-(3-ethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[3-(3-t-butylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-methylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(phenoxy)phenyl][[3(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[[3-(cyclohexylmethoxy)phenyl]-amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50 (2R)-3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-

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- (pentafluoroethyl)-phenyl)methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-isopropylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(4-fluorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(heptafluoropropyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[3-(3-ethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-t-butylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[3-(3-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[[3-(phenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethylthio)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[cyclohexylmethoxy]phenyl]-amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(heptafluoropropyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[3-(3-cyclopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(4-fluorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-3-propanol;
- 10 (2R)-3-[[3-(4-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[2-fluoro-5-(trifluoro-methyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[3-(phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-[3-(N,N-dimethylamino,phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-3-propanol;
- (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
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- (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 5 (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(3-difluoromethoxyphenoxy)phenyl][2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(3-trifluoromethoxyphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[[3-(3-isopropylphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(3-cyclopropylphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (2R)-3-[[[3-(3-(2-furyl)phenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[[3-(2,3-dichlorophenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(4-fluorophenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[3-(4-methylphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[3-(2-fluoro-5-bromophenoxy)phenyl][2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 50

- 5 (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 10 (2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
- 15 (2R)-3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- 20 (2R)-3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 25 (2R)-3-[[3-(phenoxy)phenyl][[2-fluoro-4-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- 30 (2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 35 (3R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 40 (2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 45 (2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
- (2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
- 50

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(2R)-3-[[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;

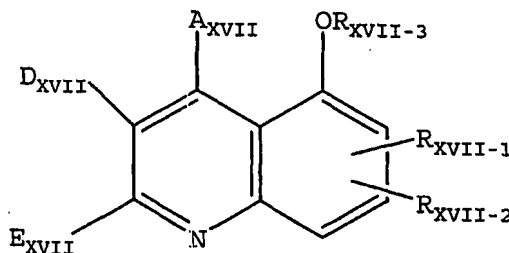
5 (2R)-3-[[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;

(2R)-3-[[[3-(3-difluoromethoxyphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;

10 (2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol; and

15 (2R)-3-[[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol.

Another class of CETP inhibitors that finds utility with the present invention consists of quinolines of Formula XVII



Formula XVII

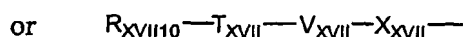
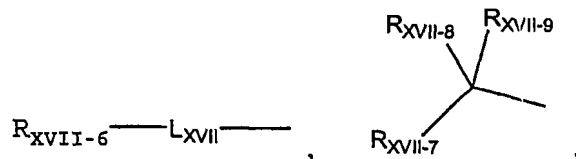
and pharmaceutically acceptable forms thereof, wherein:

25 A<sub>XVII</sub> denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with up to five identical or different substituents in the form of a halogen, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy or a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy containing up to 7 carbon atoms each, or in the form of a group according to the formula -NR<sub>XVII-4</sub>R<sub>XVII-5</sub>, wherein

30 R<sub>XVII-4</sub> and R<sub>XVII-5</sub> are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms,

D<sub>XVII</sub> denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with a phenyl, nitro, halogen, trifluoromethyl or trifluoromethoxy, or a radical according to the formula

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wherein

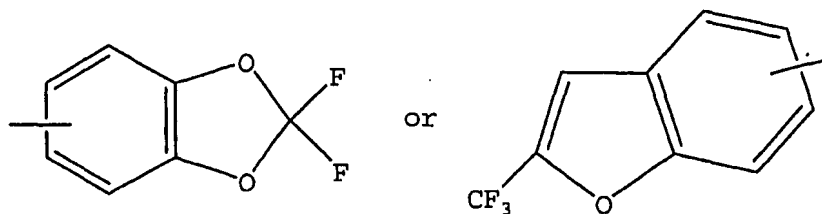
- 5  $R_{XVII-6}$ ,  $R_{XVII-7}$ ,  $R_{XVII-10}$  denote, independently from one another, a cycloalkyl containing 3 to 6 carbon atoms, or an aryl containing 6 to 10 carbon atom or a 5- to 7-membered, optionally benzo-condensed, saturated or unsaturated, mono-, bi- or tricyclic heterocycle containing up to 4 heteroatoms from the series of S, N and/or O, wherein the rings are optionally substituted, in the case of the nitrogen-containing rings
- 10 also via the N function, with up to five identical or different substituents in the form of a halogen, trifluoromethyl, nitro, hydroxyl, cyano, carboxyl, trifluoromethoxy, a straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl containing up to 6 carbon atoms each, an aryl or trifluoromethyl-substituted aryl containing 6 to 10 carbon atoms each, or an optionally benzo-condensed, aromatic 5- to 7-membered
- 15 heterocycle containing up to 3 heteroatoms from the series of S, N and/or O, and/or in the form of a group according to the formula  $-OR_{XVII-11}$ ,  $-SR_{XVII-12}$ ,  $-SO_2R_{XVII-13}$ , or  $-NR_{XVII-14}R_{XVII-15}$ ;

- $R_{XVII-11}$ ,  $R_{XVII-12}$ , and  $R_{XVII-13}$  denote, independently from one another, an aryl containing 6 to 10 carbon atoms, which is in turn substituted with up to two identical or
- 20 different substituents in the form of a phenyl, halogen or a straight-chain or branched alkyl containing up to 6 carbon atoms,

$R_{XVII-14}$  and  $R_{XVII-15}$  are identical or different and have the meaning of  $R_{XVII-4}$  and  $R_{XVII-5}$  given above, or

$R_{XVII-6}$  and/or  $R_{XVII-7}$  denote a radical according to the formula

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$R_{XVII-8}$  denotes a hydrogen or halogen, and

$R_{XVII-9}$  denotes a hydrogen, halogen, azido, trifluoromethyl, hydroxyl,

5 trifluoromethoxy, a straight-chain or branched alkoxy or alkyl containing up to 6 carbon atoms each, or a radical according to the formula  $NR_{XVII-16}R_{XVII-17}$ ;

$R_{XVII-16}$  and  $R_{XVII-17}$  are identical or different and have the meaning of  $R_{XVII-4}$  and  $R_{XVII-5}$  above; or

10  $R_{XVII-8}$  and  $R_{XVII-9}$  together form a radical according to the formula  $=O$  or  $=NR_{XVII-18}$ ;

$R_{XVII-18}$  denotes a hydrogen or a straight-chain or branched alkyl, alkoxy or acyl containing up to 6 carbon atoms each;

15  $L_{XVII}$  denotes a straight-chain or branched alkylene or alkenylene chain containing up to 8 carbon atoms each, which are optionally substituted with up to two hydroxyl groups;

$T_{XVII}$  and  $X_{XVII}$  are identical or different and denote a straight-chain or branched alkylene chain containing up to 8 carbon atoms; or

$T_{XVII}$  and  $X_{XVII}$  denotes a bond;

$V_{XVII}$  denotes an oxygen or sulfur atom or  $-NR_{XVII-19}$ ;

20  $R_{XVII-19}$  denotes a hydrogen or a straight-chain or branched alkyl containing up to 6 carbon atoms or a phenyl;

25  $E_{XVII}$  denotes a cycloalkyl containing 3 to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally substituted with a cycloalkyl containing 3 to 8 carbon atoms or a hydroxyl, or a phenyl, which is optionally substituted with a halogen or trifluoromethyl;

$R_{XVII-1}$  and  $R_{XVII-2}$  are identical or different and denote a cycloalkyl containing 3 to 8 carbon atoms, hydrogen, nitro, halogen, trifluoromethyl, trifluoromethoxy, carboxy, hydroxy, cyano, a straight-chain or branched acyl, alkoxycarbonyl or alkoxy with up to 6 carbon atoms, or  $NR_{XVII-20}R_{XVII-21}$ ;

$R_{XVII-20}$  and  $R_{XVII-21}$  are identical or different and denote hydrogen, phenyl, or a straight-chain or branched alkyl with up to 6 carbon atoms; and or

$R_{XVII-1}$  and/or  $R_{XVII-2}$  are straight-chain or branched alkyl with up to 6 carbon atoms, optionally substituted with halogen, trifluoromethoxy, hydroxy, or a straight-chain or branched alkoxy with up to 4 carbon atoms, aryl containing 6-10 carbon atoms optionally substituted with up to five of the same or different substituents selected from halogen, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, straight-chain or branched alkyl, acyl, hydroxyalkyl; alkoxy with up to 7 carbon atoms and  $NR_{XVII-22}R_{XVII-23}$ ;

$R_{XVII-22}$  and  $R_{XVII-23}$  are identical or different and denote hydrogen, phenyl or a straight-chain or branched alkyl up to 6 carbon atoms; and/or

$R_{XVII-1}$  and  $R_{XVII-2}$  taken together form a straight-chain or branched alkene or alkane with up to 6 carbon atoms optionally substituted with halogen, trifluoromethyl, hydroxy or straight-chain or branched alkoxy with up to 5 carbon atoms;

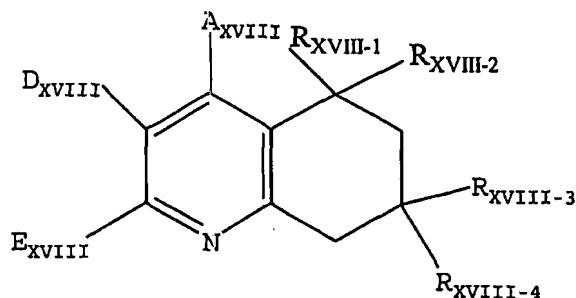
$R_{XVII-3}$  denotes hydrogen, a straight-chain or branched acyl with up to 20 carbon atoms, a benzoyl optionally substituted with halogen, trifluoromethyl, nitro or trifluoromethoxy, a straight-chained or branched fluoroacyl with up to 8 carbon atoms and 7 fluoro atoms, a cycloalkyl with 3 to 7 carbon atoms, a straight chained or branched alkyl with up to 8 carbon atoms optionally substituted with hydroxyl, a straight-chained or branched alkoxy with up to 6 carbon atoms optionally substituted with phenyl which may in turn be substituted with halogen, nitro, trifluoromethyl, trifluoromethoxy, or phenyl or a tetrazol substituted phenyl, and/or an alkyl that is optionally substituted with a group according to the formula  $-OR_{XVII-24}$ ;

$R_{XVII-24}$  is a straight-chained or branched acyl with up to 4 carbon atoms or benzyl.

Compounds of Formula XVII are disclosed in WO 98/39299, the entire disclosure is incorporated by reference.

Another class of CETP inhibitors that finds utility with the present invention consists of 4-Phenyltetrahydroquinolines of Formula XVIII

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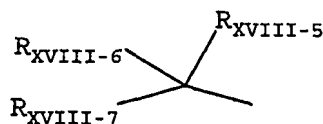


Formula XVIII

5 , N oxides thereof, and pharmaceutically acceptable forms thereof, wherein:

$A_{XVIII}$  denotes a phenyl optionally substituted with up to two identical or different substituents in the form of halogen, trifluoromethyl or a straight-chain or branched alkyl or alkoxy containing up to three carbon atoms;

$D_{XVIII}$  denotes the formula



or  $R_{XVIII-8}-CH_2-O-CH_2-$ ;

10

$R_{XVIII-5}$  and  $R_{XVIII-6}$  are taken together to form  $=O$ ; or

$R_{XVIII-5}$  denotes hydrogen and  $R_{XVIII-6}$  denotes halogen or hydrogen; or

$R_{XVIII-5}$  and  $R_{XVIII-6}$  denote hydrogen;

$R_{XVIII-7}$  and  $R_{XVIII-8}$  are identical or different and denote phenyl, naphthyl,

15 benzothiazolyl, quinoliny, pyrimidyl or pyridyl with up to four identical or different substituents in the form of halogen, trifluoromethyl, nitro, cyano, trifluoromethoxy, -  
 $SO_2-CH_3$  or  $NR_{XVIII-9}R_{XVIII-10}$ ;

$R_{XVIII-9}$  and  $R_{XVIII-10}$  are identical or different and denote hydrogen or a straight-chained or branched alkyl of up to three carbon atoms;

20  $E_{XVIII}$  denotes a cycloalkyl of from three to six carbon atoms or a straight-chained or branched alkyl of up to eight carbon atoms;

$R_{XVIII-1}$  denotes hydroxy;

$R_{XVIII-2}$  denotes hydrogen or methyl;



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$R_{XVIII-3}$  and  $R_{XVIII-4}$  are identical or different and denote straight-chained or branched alkyl of up to three carbon atoms; or

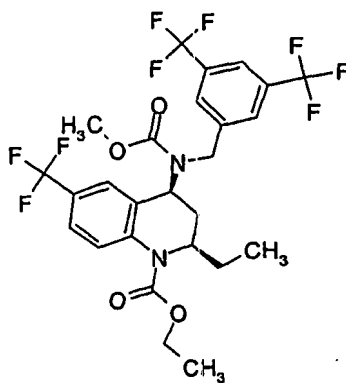
$R_{XVIII-3}$  and  $R_{XVIII-4}$  taken together form an alkenylene made up of between two and four carbon atoms.

- 5        Compounds of Formula XVIII are disclosed in WO 99/15504, the entire disclosure of which is incorporated by reference.

10        Emulsion pre-concentrates of CETP inhibitors, formulated as described above, are encapsulated in soft gelatin capsules, or are encapsulated in hard gelatin or non-gelatin capsules. If encapsulated in hard gelatin or non-gelatin capsules, it is preferred that the seam between the two capsule shell pieces be sealed, for example with a strip of gelatin, to prevent leakage. Encapsulation in soft-gelatin is well-known and is described in "The Theory and Practice of Industrial Pharmacy", by L. Lachman, H. Lieberman, and J. Kanig, Lea and Febiger, publisher, 3<sup>rd</sup> Edition, 1986.

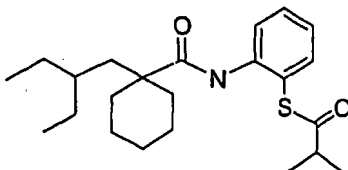
- 15        The invention is further disclosed and described in the following examples, which are illustrative as opposed to limiting. In the examples, "mgA" is an abbreviation for "milligrams of active drug", the weight being expressed in mg of the non-salt, free acid or base. Other commonly employed and understood abbreviations have been employed: Me, methyl; Cmpd, Compound; In the  
20        examples, the following shorthand notation means the corresponding structure listed and/or named below:

- 25        Compound A - [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, with a Clog P of 7.45 and having the following structure:



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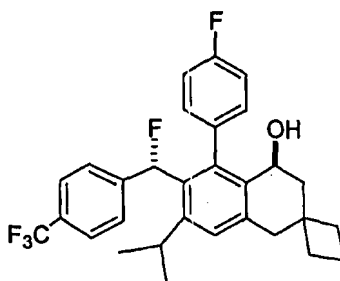
- 5 Compound B, Propanethioic acid, 2-methyl-, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester with a Clog P of 7.15 having the structure:



10

15

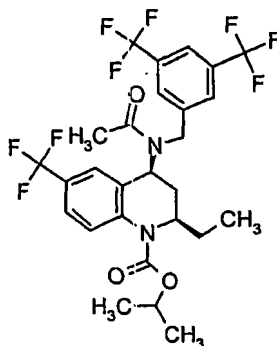
- Compound C, (S,S)-4'-(4-fluorophenyl)-3'-[fluoro[4-(trifluoromethyl)phenyl]methyl]-5',8'-dihydro-2'-(1-methylethyl)-spiro[cyclobutane-1,7'(6'H)-quinolin]-5'-ol, with a Clog P of 8.93 and having the following structure:



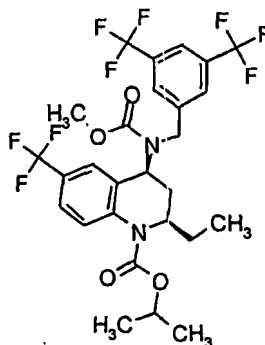
20

- 25 Compound D [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, with a Clog P of 6.52 and the following structure:

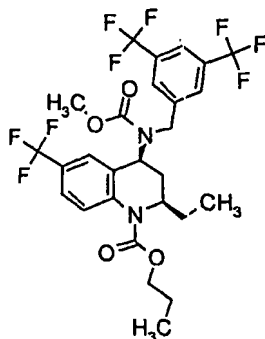
-117-



- Compound E - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, with a Clog P of 7.76 and having the following structure:



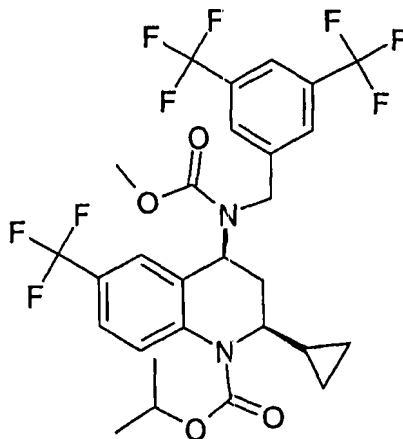
- Compound F - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester, having a Clog P of 7.98 and having the following structure:



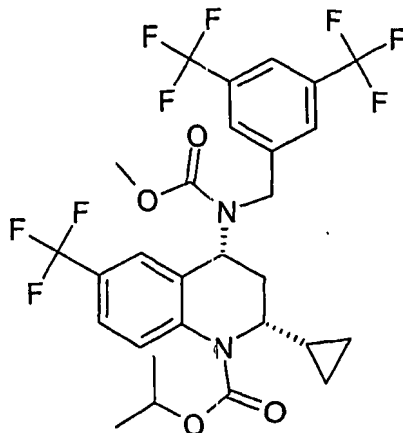
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Compound G - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, having a Clog P of 7.58 and having the following structure:

5

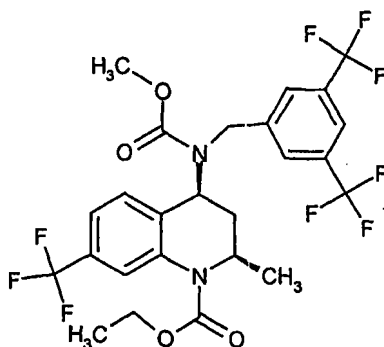


10 Compound H - [2S, 4R] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, having a Clog P of 7.58 and having the following structure:

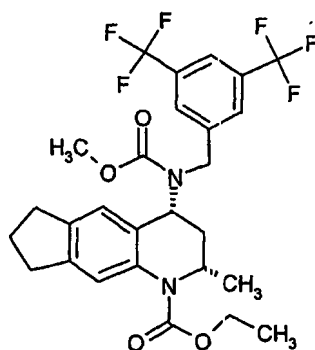


15 Compound I - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 6.92 and having the following structure:

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- 5 Compound J [2S, 4R] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-2,3,4,6,7,8-hexahydro-cyclopenta[g]quinoline-1-carboxylic acid ethyl ester, having a Clog P of 7.05 and having the following structure:

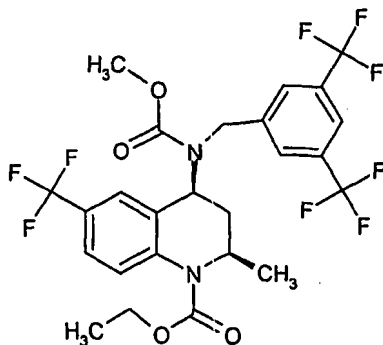


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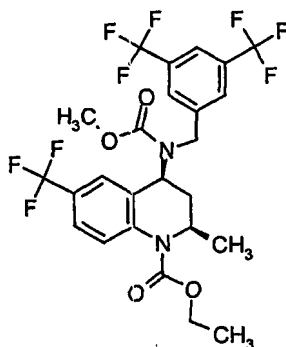
Compound K - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 6.92 and having the following structure:

15

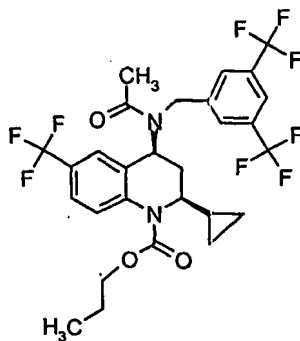
-120-



Compound L - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 6.92 and having the following structure:

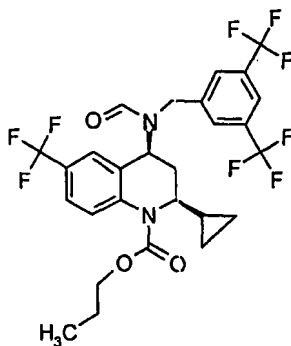


Compound M - [2R, 4S] 4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester, having a Clog P of 6.56 and having the following structure:

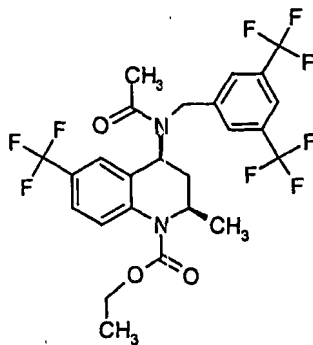


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- 5 Compound N - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester, having a Clog P of 6.33 and having the following structure:



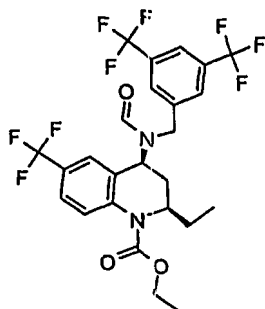
- 10 Compound O - [2R, 4S] 4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 5.68 and having the following structure:



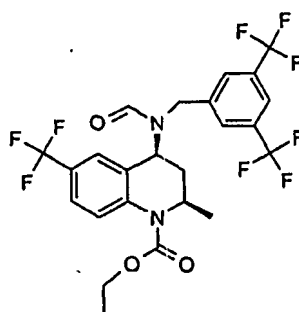
15

- 20 Compound P - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 5.97 and having the following structure:

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- Compound Q - [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, having a Clog P of 5.45 and having the following structure:



### 10 Example 1

This Example (and Examples 2 through 5) illustrates making a composition according to the invention and using it to make softgel capsules containing it.

- Capmul<sup>®</sup> MCM was heated to 55 °C and mixed. To a 2 liter glass beaker was added 277 gm of Miglyol<sup>®</sup> 812, 510 gm of triacetin, 318 gm of Polysorbate 80, and 442 gm of Capmul<sup>®</sup> MCM. After stirring for one hour, this solution was added to 161 gm Compound A and the resulting mixture stirred at ambient temperature for 8 hours with scraping of walls as needed. It was then filtered to remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 1.

- The above 100 mgA/mL fill was encapsulated into #10 oval and #5 oval softgels to provide fill volumes of 0.6 mL and 0.3 mL respectively. The doses per softgel are therefore 60 mgA and 30 mgA, respectively. The shell was prepared from gelatin, glycerin, and water.



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Table 1

<b>Ingredient</b>	<b>mg/g</b>
Compound A	94
Miglyol® 812	162
Triacetin	299
Polysorbate 80	186
Capmul® MCM	259

**Example 2**

5

Capmul® MCM was heated to 55°C and mixed. Cremophor® RH40 was also heated to 65°C with stirring. Then 539 g of Miglyol 812, 998 g of triacetin, 608 g of Cremophor® RH40, and 860 g of Capmul® MCM were combined and mixed for 20 min.

To this mixture was then added 312 gm of Compound D and the resulting mixture stirred at ambient temperature for 3 hours with scraping of walls as needed. It was then filtered to remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 2.

The above 100 mgA/mL fill was encapsulated into #2 and #5 oval softgels to provide fill volumes of 0.1 mL and 0.3 mL, respectively. The doses per softgel were therefore 10 and 30 mgA, respectively. The shell was prepared from gelatin, glycerin, and water.

Table 2

<b>Ingredient</b>	<b>mg/g</b>
Compound D	94
Miglyol 812	163
Triacetin	301
Cremophor RH40	183
Capmul MCM	259

20

**Example 3**

Capmul® MCM was heated to 55°C and mixed. Alpha-tocopheryl polyethyleneglycol 1000 succinate (TPGS) was also heated to 55°C with stirring. Then 264 gm of Miglyol® 812, 333 gm of propylene carbonate, 103 gm of TPGS, and 562 gm of Capmul® MCM were combined and mixed for 1 hr. This mixture was then added to 130.4 gm of Compound A and the resulting mixture stirred at ambient temperature for 8 hours with scraping of walls as needed. It was then filtered to

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remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 3.

- The above 100 mgA/mL fill was encapsulated into #11 oblong softgels to provide a fill volume of 0.6 mL. The dose per softgel is therefore 60 mgA. The shell
- 5 was prepared from gelatin, glycerin, and water.

Table 3

Ingredient	mg/g
Compound A	94
Miglyol® 812	164
Propylene carbonate	207
Alpha-tocopheryl polyethyleneglycol 1000 succinate	185
Capmul® MCM	350

10

**Example 4**

- Capmul® MCM was heated to 55°C and mixed. Then 264 gm of Miglyol® 812, 333 gm of propylene carbonate, 303 gm of Polysorbate 80 and 562 gm of Capmul® MCM were combined and mixed for 1 hr. This mixture was then added to 130.5 gm of Compound A and the resulting mixture stirred at ambient temperature for 8 hours with scraping of walls as needed. It was then filtered to remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 4.
- 15

- The above 100 mgA/mL fill was encapsulated into #11 oblong softgels to provide a fill volume of 0.6 mL. The dose per softgel is therefore 60 mgA. The shell was prepared from gelatin, glycerin, and water.
- 20

25

Table 4

Ingredient	mg/g
Compound A	95
Miglyol® 812	163
Propylene carbonate	206
Polysorbate 80	188
Capmul® MCM	348

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**Example 5**

Capmul® MCM was heated to 55°C and mixed. Then 271 gm of Miglyol® 812, 250 gm of triacetin, 779 gm of Polysorbate 80 and 217 gm of Capmul® MCM were combined and mixed for 20 min. This mixture was then added to 75.7 gm of  
5 COMPOUND A and the resulting mixture stirred at ambient temperature for 8 hours with scraping of walls as needed. It was filtered to remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 5.

The above 50 mgA/mL fill was encapsulated into #11 oblong softgels to provide a fill volume of 0.6 mL. The dose per softgel is therefore 30 mgA. The shell  
10 was prepared from gelatin, glycerin, and water.

Table 5

Ingredient	mg/g
Compound A	48
Miglyol® 812	170
Triacetin	157
Polysorbate 80	489
Capmul® MCM	136

15

**Example 6**

This Example (and Example 7) illustrates the composition of fills according to the invention. The amounts (in mg) of each component in the fill per gram of fill are set  
20 forth in Table 6. This fill was prepared at a concentration of 50 mgA/mL in a manner similar to that described in Examples 1-5 but at a small volume for dog PK studies. It could be prepared at a larger scale for encapsulation into #11 oblong softgels to provide a fill volume of 0.6 mL and a dose of 30 mgA.

25

Table 6

Composition	mg/g
Compound A	48
Miglyol® 812	143
Triacetin	143
Cremophor® RH 40	381
Capmul® MCM	286

**Example 7**

5           The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 7. The fill was prepared at a concentration of 150 mgA/mL in a manner similar to that described in Examples 1-5, but at a small volume for dog PK studies. It could be prepared at a larger scale for encapsulation into #11 oblong softgels to provide a fill volume of 0.6 mL and a dose of 90 mgA.

10

Composition	mg/g
Compound A	142
Miglyol® 812	86
Ethyl lactate	429
Cremophor® RH 40	257
Capmul® MCM	86

**Example 8**

15

To 80.1 g of Compound A was added 1451 gm Miglyol® 812. The resulting mixture was stirred at ambient temperature for 8 hours with scraping of walls as needed. It was filtered to remove gross particulates. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 8.

20

The above 50 mgA/mL fill was encapsulated into #11 oblong and #4 oval softgels to provide fill volumes of 0.6 mL and 0.2 ml, respectively. The doses per softgel were therefore 30 and 10 mgA, respectively. The shell was prepared from gelatin, glycerin, and water.

25

30

Table 8

Ingredient	mg/g
Compound A	52
Miglyol® 812	948

**Example 9**

5

This example describes the determination of solubility of CETP inhibitors in excipients and emulsion preconcentrates and also an initial assessment of emulsion quality (Table 9a-9d).

10 The solubility of CETP inhibitors in excipients and in formulations was determined by adding an excess of compound to the medium in question. The mixture was agitated by rotation over a period of days at ambient temperature until the concentration in solution had reached an equilibrium as judged by similar measurements for consecutive time points. Concentrations were measured by filtration of aliquots with a PTFE syringe filter and assay by HPLC as described in

15 Example 11.

For CETP inhibitors where quantities were limited, an estimate of solubility was obtained by addition of vehicle to a known quantity of the compound and mixing in an ultrasonicator bath for 90 minutes, followed by overnight equilibration at ambient temperature. Addition of vehicle was repeated until a solution was achieved.

20 The extent of emulsification was determined by mixing the preconcentrate and water in a ratio of 1:100 and 1:10 by gentle inversion (5 x), visual inspection, and examination under an optical microscope, using a polarizing filter to check for the appearance of crystals. Droplet size determined by this approach is expressed as the upper limit for the average droplet size, since submicron droplets cannot be detected

25 by this method.

The results in Table 9a show that the solubility of Compound A in Miglyol® 812 is only sufficient for a 50 mgA/mL fill (30 mgA in a 0.6 mL softgel), while cosolvents such as triacetin and propylene carbonate provide ca. 4x higher solubility and those such as ethyl lactate and dimethyl isosorbide nearly double those levels. Solubility and

30 emulsification data for preconcentrate solutions of Compound A is shown in Table 9c. Use of propylene carbonate and triacetin as cosolvents allow solubilities sufficient in some cases for a 100 mgA/mL self-emulsifying fill. (e.g., Formulations M, O, Q, and R, see Table 9c)

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Higher levels of surfactants are often required to yield self-microemulsifying formulations and in these cases solubilities only permit in general a 50 mgA/mL fill using triacetin as the cosolvent (e.g. Formulation EE, Y, and PP). Use of propylene carbonate or ethyl lactate as cosolvent can permit a 100mgA/mL fill (e.g., Formulations A, B, XX, YY, and ZZ) that has sufficient surfactant to yield microemulsions. However, triacetin has the advantage of good precedence in oral dosage forms (and has GRAS status). Dynamic light scattering was utilized to further characterize the sub-micron particle size distribution for microemulsions as described in Example 10.

The solubility in ethyl lactate permits a self-emulsifying 150 mgA/mL fill to be prepared (e.g Formulation WW). However, the solubilities of emulsion preconcentrates shown in Table 9a and 9c cannot reliably be predicted based on the solubilities of the components alone. This is exemplified by formulation WW (Table 9c), which exhibits considerably greater solubility than the corresponding formulation using dimethyl isosorbide (Formulation AAA), although the opposite would have been predicted based on solubilities in the individual cosolvents. Also, lack of data for excipients that are solids at room temperature also hinders prediction.

All of the emulsions prepared from these formulations exhibited good physical stability, i.e. there was no sign of crystallization or change in particle size based on microscopic examination after standing overnight at ambient temperature.

Results obtained for other CETP inhibitors are shown in Tables 9b and 9d. In case of Compound D (Table 9b), the average emulsion particle size is < 5 microns.

Table 9a. Equilibrium Solubility Data for Compound A in Oils, Solvents, and Surfactants

Vehicle	HLB	Solubility (mgA/ml)
Water		< 0.00004
Oleic acid		8.5
Maisine 35-1	4	9
Peceol	3	10
Olive oil		17
Plurol Oleique CC 497	6	17

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Cremophor® EL		20
Polysorbate 80 (Tween 80)	15	23
Labrafil® M 1944	4	26
Labrafil® M 2125	4	27
Tagat TO (Polyoxyethylene glycerol trioleate)	11	32
Pluronic® L-44		36
Capmul® MCM	6	41
Labrasol®	14	41
Miglyol® 812		65
Lauroglycol FCC	4	70
Glycofurol		99
Caprylic acid		145
Transcutol P		174
Propylene carbonate		227
Triacetin		235
Triethyl citrate		240
peppermint oil		266
Ethyl lactate		400
Dimethylisosorbide		439
N-methyl-2-pyrrolidone		813

5

Table 9b: Equilibrium Solubility Data for Other CETP inhibitors

Vehicle	Solubility (mgA/ml)	
	Compound D	Compound E
Olive oil	13	39
Olive oil /Cremophor® EL 80/20	14	
Cremophor® EL	18	
Miglyol® 812/Cremophor® EL 80/20	51	
Capmul® MCM	58	
Miglyol® 812	61	167

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Miglyol®/propylene carbonate/Cremophor® EL (60/20/20)	208	394
Triacetin	239	

Table 9c. Solubility and emulsification data for Compound A in preconcentrates\*

5

Formul. No.	Composition (% v/v)			Solubility (mgA/mL)	Ave Droplet Size (μ) (1:100 dilution)
	Miglyol® 812	Cosolvent*	Surfactants		
			Vitamin E TPGS/ Capmul® MCM		
A	20	20 P.C.	20/40	145	<1
H	20	20 triacetin	20/40	113	<2
I	20	30 P.C.	20/30	189	<2
S	10	30 triacetin	20/40	131	<5
			Polysorbate 80/ Capmul® MCM		
B	20	20 P.C.	20/40	142	<5
O	20	30 triacetin	20/30	141	<2
EE	20	15 triacetin	50/15	64	<1
			Vitamin E TPGS/ Labrafil® M 1944 CS		
C	20	20 P.C.	20/40	114	<1
Q	10	40 triacetin	20/30	142	<2
			Gelucire® 44/14/ Capmul® MCM		
D	20	20 P.C.	20/40	151	<5
			Cremophor® RH40/ Capmul® MCM		
E	20	20 P.C.	20/40	147	<1
M	20	30 triacetin	20/30	145	<1
R	20	30 triacetin	35/15	122	<1
SS	0	28 triacetin	30/42	108	<1
PP	17	13 triacetin	39/31	77	<1
Y	20	10 triacetin	50/20	67	<1
WW	11	50 ethyl lactate	29/10	203	<2
XX	11	40 ethyl lactate	29/20	159	<1



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YY	16	35 ethyl lactate	39/10	142	<1
ZZ	22	29 ethyl lactate	19/30	145	<1
AAA	11	47 dimethyl isosorbide	31/11	157	<1

\* P.C. = propylene carbonate

- 5 Table 9d. Solubility and emulsification data for other CETP Inhibitor pre-concentrates

Compound	Composition (% v/v)			Solubility (mgA/mL)	Ave Droplet Size (μ) (1:100 dilution)
	Miglyol® 8 12	Triacetin	Surfactants		
			Polysorbate 80/ Capmul® MCM		
Compound B*	20	30	20/30	≥ 100	<5
Compound C*	6	55	15/24	≥ 30	<5
Compound E	22	27	20/31	308	<2
			Cremophor® RH40/ Capmul® MCM		
Compound D	20	30	20/30	172	<5

\* Amorphous solids

10

### Example 10

- Preliminary particle size analysis data has been obtained on selected formulations using a dynamic light scattering particle size analyzer (ZetaPals, Brookhaven Instruments, Inc.) for measurement of sub-micron particle distribution. The formulation solutions were diluted 1:100 in HPLC-grade water (previously filtered through a 0.22 μm syringe filter). The resulting mixture was gently inverted five times to create the emulsion. Each emulsion sample was then analyzed at a temperature of 37°C. Triplicate measurements were made at each time point (0, 30 min).

The results shown in Table 10 confirm that formulations O, Q and R are self-emulsifying formulations with a mean particle size above 100 nm. Formulations

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- such as A and B have mean particle sizes in the microemulsion range but with significant populations of larger particles and are slightly turbid. Formulation EE is very slightly turbid with a trace of larger particles. Use of Cremophor® RH 40 as the high HLB surfactant yielded formulations Y, PP, XX, and ZZ that form transparent microemulsions with all particles smaller than ca. 100 nm, as is the case for Neoral®. Only formulation Y showed a stable unimodal distribution that did not change, even with stirring.

10 Table 10a. Dynamic Light Scattering Particle Size Analysis of Emulsions from Compound A Self-Emulsifying Formulations\*

Form.	Pre-concentrate Composition (% v/v)	Mean Diam. (nm)	Distribution #		
			Peak 1	Peak 2	Peak 3
A	Miglyol® 812/propylene carbonate/Vitamin E-TPGS/Capmul® MCM (20/20/20/40)	78.6	22	73	349
B	Miglyol® 812/propylene carbonate/Polysorbate 80/Capmul® MCM (20/20/20/40)	45.3	33	217	
C	Miglyol® 812/propylene carbonate/Vitamin E-TPGS/Labrafil M® 1944 CS (20/20/20/40)	21.6	17	38	(197)
O	Miglyol® 812/Triacetin/Polysorbate 80/Capmul® MCM (20/30/20/30)	256.6	257		
Q	Miglyol® 812/Triacetin/Vitamin E-TPGS/Labrafil M® 1944 CS (10/40/20/30)	440.9	259	537	
R	Miglyol® 812/Triacetin/Cremophor® RH40/Capmul MCM (20/30/35/15)	245.2	245		
X	Neoral®/propylene carbonate (90:10)	19.0	11	29	
Y	Miglyol® 812/Triacetin/Cremophor® RH40/Capmul® MCM (20/10/50/20)	22.3	22		
EE	Miglyol® 812/Triacetin/Polysorbate 80/Capmul® MCM (20/15/50/15)	19.6	13	64	(220)

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PP	Miglyol <sup>®</sup> 812/Triacetin/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (17/13/39/31)	27.1	27		
SS	Triacetin/Cremophor <sup>®</sup> RH40 /Capmul <sup>®</sup> MCM (28/30/42)	32.4	26	(116)	
WW	Miglyol <sup>®</sup> 812/Ethyl lactate/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (11/50/29/10)	293.8	324		
XX	Miglyol <sup>®</sup> 812/Ethyl lactate/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (11/40/29/20)	24.9	22	(107)	
YY	Miglyol <sup>®</sup> 812/Ethyl lactate/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (16/35/39/10)	31.5	28	(135)	
ZZ	Miglyol <sup>®</sup> 812/Ethyl lactate/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (22/29/19/30)	36.3	34	(103)	
	Neoral <sup>®</sup>	27.4	27	(65)	

# Parentheses indicate trace levels.

\* Measured immediately after preparation unless indicated otherwise

5

Table 10b. Dynamic Light Scattering Particle Size Analysis of Emulsions prepared for Other Compounds

Cmpd.	Conc. (mg/mL)	Pre-Concentrate Composition (% v/v)	Mean Diam. (nm)#	
			Initial*	30 min.*
D	100	Miglyol <sup>®</sup> 812/Triacetin/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (20/30/20/30)	—	182 ± 17 (3)
E	100	Miglyol <sup>®</sup> 812/Triacetin/ Polysorbate 80/Capmul <sup>®</sup> MCM (22/27/20/31)	181	175
E	200	Miglyol <sup>®</sup> 812/Triacetin/ Polysorbate 80/Capmul <sup>®</sup> MCM (22/27/20/31)	239 ± 17 (4)	251 ± 45 (4)

10 # Number of samples in parentheses

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\* Time after preparation of emulsion

### Example 11

5

The fills prepared in the above examples were hand-filled into hydrophobic softgel shells and heat sealed, and then placed on stability under accelerated conditions in sealed HPDE bottles with child-resistant caps. The fills were assayed at intervals by dilution of aliquots into acetonitrile and gradient HPLC analysis on a

10 Water Symmetry C-8 column (3.9 x 150 mm, 5 micron) at 30°C at a flow rate of 1 mL/min. The mobile phase program was a 25 minute gradient from 100 % A to 50% A/50 % B (A = 400/300/300/0.8 v/v DI H<sub>2</sub>O/Acetonitrile/2-Propanol/Phosphoric Acid and B = 2-Propanol), followed by a 5 minute hold at this condition and a 10 minute gradient to the initial condition. The detection method was UV absorbance at 210  
15 nm.

There was no impurity formed at  $\geq 0.1$  % peak area vs. parent for any formulation in Table 11. There was no sign of crystallization in the fill under any condition based on microscopic examination. There was also no indication of seal leakage.

20 Disintegration times in water at 37°C were less than 15 min for Formulations A, B, and O after storage under accelerated conditions for 6 weeks.

Formulation O softgels of Compound A manufactured by machine have been shown to be stable for 9 months under accelerated conditions. Formulation M softgels of Compound D have been shown to be stable for 6 months under

25 accelerated conditions.

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Table 11. Accelerated Stability data for selected formulations of Compound A in hand- filled soft gels

Test	Assay of Fill					
	Assay of Fill Potency					
Formulation #	A	B	C	E	M	O
Initial	100.6 ± 0.6	99.4 ± 0.7	101.3 ± 0.8	102.0 ± 0.1	101.6 ± 0.2	102.6 ± 0.6
1 Week						
5°C/75%RH	101.8 ± 0.8	99.5 ± 2.3	99.1 ± 0.4	101.5 ± 0.4		
30°C/60%RH	100.8 ± 0.6	98.8 ± 0.6	100.5 ± 0.7	101.1 ± 0.1		
40°C/75%RH	101.4 ± 0.5	98.6 ± 1.4	99.7 ± 0.5	102.6 ± 0.1		
3 Week OR 4 Week	*	*				
5°C/75%RH	99.9 ± 0.4	99.0 ± 0.3	99.3 ± 1.0	100.5 ± 0.6	100.6 ± 0.5	101.1 ± 0.6
30°C/60%RH	100.7 ± 0.8	98.4 ± 0.7	100.0 ± 0.6	99.9 ± 0.5	100.3 ± 0.6	101.4 ± 1.3
40°C/75%RH	101.3 ± 0.3	100.7 ± 1.0	101.8 ± 0.5	102.3 ± 0.4	102.9 ± 0.6	101.7 ± 0.2
6 Week						
5°C/75%RH	100.7 ± 0.8	100.7 ± 0.1	98.4 ± 0.3	100.0 ± 0.3	101.2 ± 0.5	101.9 ± 0.2
30°C/60%RH	100.4 ± 0.8	100.5 ± 0.4	101.1 ± 0.6	101.1 ± 0.2	101.6 ± 0.6	101.9 ± 0.8
40°C/75%RH	102.4 ± 0.7	102.1 ± 1.0	102.5 ± 0.4	102.7 ± 0.7	101.6 ± 0.5	101.9 ± 0.9

\* 4 Week time point.

**Example 12**

Fills were prepared as described in above examples and then encapsulated in #00 hard gelatin capsules. Male Beagle dogs (n=6) between the ages of 2-5 and weighing 6-12 kg were dosed with capsules followed by 50 mL of water. Dogs were also dosed with 30 mgA Miglyol® 812 softgels and aqueous, crystalline drug suspension. The dogs were either fasted or fed just prior to dosing with 14 g of dry dog food and 8 gm olive oil. The same set of dogs were used for all formulations, except where indicated. Blood samples were obtained from the jugular vein of each dog at 0, 0.5, 1, 2, 3, 4, 6, 8 and 12 hr and analyzed by acidifying the plasma, solid phase extraction, and analysis by LC/MS/MS with a lower limit of quantitation of 25 ng/mL.

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The results, in Table 12a and 12b are shown in terms of Area Under the Curve (AUC), C<sub>max</sub>, the maximum concentration of drug measured in the plasma, and T<sub>max</sub>, the time in hours it took to reach C<sub>max</sub>. Unless otherwise indicated, results are for the fasted state. Miglyol® softgels have a very low fasted exposure and thus a high food effect. The fasted exposure is higher than that for crystalline suspension, while the fed exposure using this high oil meal is the same. Thus Miglyol softgels provide a lower food effect than crystalline drug. At the same dose of 90 mgA, formulations such as A, O, and C that include surfactants and cosolvent have much higher fasted exposures and only a ca. 3x food effect. The fed exposures are also higher than for Miglyol® 812 softgels and crystalline drug. Poorer fasted exposure was obtained for Formulation WW, which contains a high level of ethyl lactate as a cosolvent.

The transparent self-microemulsifying formulations EE and PP at a dose of 30 mgA have a food effect of only 2.2-2.4. For the stable, monodisperse microemulsion Y there is a much higher fasted exposure at 30 mgA than for the self-emulsifying formulation O. The fasted exposure for Y was the same as the fed, i.e. there was no food effect.

Similar results were obtained for formulation M for Compound D (Table 12b) as were observed for the same formulation of Compound A.

Table 12a. Pharmacokinetic results of Compound A Formulations in dogs

#	Formulation Composition (v/v)	n*	Conc. (mg/mL)	Dose (mg)	AUC 0- 12h ( $\mu\text{g}^*\text{h/mL}$ )	Cmax ( $\mu\text{g/mL}$ )	Tmax (hr)
	Miglyol® 812 <u>soft gels</u>						
	Fed	4	50	90	$3.0 \pm 2.0$	$0.77 \pm 0.48$	2.0
		6	50	90	$0.6 \pm 0.3$	$0.2 \pm 0.14$	3.7
	Crystalline drug suspension in 0.1% Polysorbate 80/ 0.5% methyl cellulose	6 <sup>#</sup>	—	90	$0.16 \pm 0.14$	$0.04 \pm 0.11$	1.3
	Fed	6	—	90	$2.9 \pm 1.3$	$0.98 \pm 0.53$	2.7
A	Miglyol® 812 /Propylene carbonate/ Vitamin E-TPGS/Capmul® MCM (20/20/20/40)	6	100	90	$2.7 \pm 0.9$	$0.67 \pm 0.17$	1.2
	Fed	5	100	90	$9.6 \pm 3.4$	$2.49 \pm 1.30$	1.4
B	Miglyol® 812 /Propylene carbonate/ Polysorbate 80/Capmul® MCM (20/20/20/40)	6	100	90	$2.3 \pm 0.5$	$0.73 \pm 0.16$	1.8
C	Miglyol® 812 /propylene carbonate/ Vitamin E-TPGS/ Labrafil® M 1944 (20/20/20/40)	5	80	90	$3.4 \pm 1.3$	$1.2 \pm 0.41$	1.2
	Fed	6	80	90	$9.3 \pm 3.5$	$4.31 \pm 1.89$	1.0
I	Miglyol® 812 /Propylene carbonate/ Vitamin E-TPGS/Capmul® MCM (20/30/20/30)	6	125	90	$1.6 \pm 0.5$	$0.61 \pm 0.27$	0.9
J	Miglyol® 812 /Propylene carbonate/ Vitamin E-TPGS (20/40/40)	6	125	90	$2.0 \pm 0.8$	$0.71 \pm 0.36$	1.7
M	Miglyol® 812 /Triacetin/ Cremophor® RH40/ Capmul® MCM (20/30/20/30)	5	100	90	$2.6 \pm 1.2$	$0.73 \pm 0.26$	1.2
O	Miglyol® 812 /Triacetin/ Polysorbate 80/Capmul® MCM (20/30/20/30)	6	100	90	$2.7 \pm 0.7$	$0.97 \pm 0.36$	1.2

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	Fed	4	100	90	8.5 ± 3.6	2.7 ± 1.0	1.5
		6	100	30	1.1 ± 0.5	0.37 ± 0.22	1.0
Q	Miglyol® 812 /Triacetin/ Vitamin E-TPGS/ Labrafil® M 1944 (10/40/20/30)	5**	100	90	2.9 ± 0.8	1.1 ± 0.2	1.0
R	Miglyol® 812 /Triacetin/ Cremophor® RH40/ Capmul® MCM (20/30/35/15)	6	100	90	2.8 ± 1.2	1.0 ± 0.4	1.0
		6	50	90	4.0 ± 1.3	1.1 ± 0.4	1.5
X	Neoral®/propylene carbonate (90:10)	3	50	90	2.4 ± 1.9	0.67 ± 0.23	1.3
Y	Miglyol® 812 /Triacetin/ Cremophor® RH40/ Capmul® MCM (20/10/50/20)	6	50	90	4.6 ± 1.4	1.35 ± 0.26	1.7
		4**	50	30	4.6 ± 2.0	1.32 ± 0.60	2.0
	Fed	5	50	30	4.7 ± 1.1	1.94 ± 0.74	1.0
EE	Miglyol® 812 /Triacetin/ Polysorbate 80/ Capmul® MCM (20/15/50/15)	6	50	90	2.7 ± 1.5	0.86 ± 0.31	1.3
	Fed	5	50	30	1.7 ± 0.3	0.64 ± 0.21	1.0
		6	50	30	3.8 ± 1.2	1.6 ± 0.6	1.0
PP	Miglyol® 812 /Triacetin/ Cremophor® RH40/ Capmul® MCM (17/13/39/31)	5	50	30	1.6 ± 0.6	0.61 ± 0.18	1.2
	Fed	5	50	30	3.8 ± 0.8	1.55 ± 0.38	1.4
SS	Triacetin/Cremophor® RH40 /Capmul® MCM (28/30/42)	6	75	90	1.9 ± 1.7	0.44 ± 0.26	1.3
	Fed	4	75	90	7.3 ± 1.3	1.8 ± 0.5	1.5
WW	Miglyol® 812 /Ethyl lactate /Cremophor ®RH40 /Capmul® MCM (11/50/29/10)	5	150	90	1.5 ± 0.7	0.54 ± 0.17	0.9

\* n &lt; 6 due to emesis.

\*\* Due to emesis and outlier

# Different set of dogs



Table 12b Pharmacokinetic results for Other Compounds in dogs

Cmpd	Formulation Composition	n	Conc. (mg/mL)	Dose (mg)	AUC 0-tlast <sup>#</sup> (μg*h/mL)	Cmax (μg/mL)	Tmax (hr)
D*	Miglyol <sup>®</sup> 812 /Triacetin/ Cremophor <sup>®</sup> RH40/ Capmul <sup>®</sup> MCM (20/30/20/30)	3*	100	90	3.45 ± 0.96	0.86 ± 0.31	1.7
	Fed	4*	100	90	4.84±1.23	1.20±0.41	1.5
E	Miglyol <sup>®</sup> 812/Triacetin/ Polysorbate 80/Capmul <sup>®</sup> MCM (22/27/20/31)	4**	100	60	2.90 ± 0.67	0.20 ± 0.14	1.5

- 5    \* Emesis in 1 fasted dog (data not included) and in 4 fed dogs (included); dosed with 50 mL water.  
      \*\* Emesis in 3 dogs (included), dosed with 10 mL water. Different set of dogs from those receiving Compound D.  
      # Tlast = 24 hr for Compound D and 48 hr for Compound E.

10

**Example 13:**

- 15        This example further illustrates the determination of equilibrium solubilities of CETP inhibitors in vehicles. For experimental methods, see Example 9.

- 20        The solubility of crystalline CETP inhibitors in representative vehicles was determined by adding an excess of compound to the vehicle in question. The mixture was agitated by rotation over a period of days at ambient temperature until the concentration in solution had reached equilibrium as judged by similar measurements for consecutive time points. Concentrations were measured by filtration of aliquots with a PTFE syringe filter and assayed by HPLC.

- 25        The concentrations of CETP inhibitor in each vehicle were assayed at intervals by dilution of aliquots into acetonitrile and gradient HPLC analysis on a Water Symmetry C-8 column (3.9 x 150 mm, 5 micron) at 30 °C at a flow rate of 1 mL/min. The mobile phase program was a 25 minute gradient from 100 % A to 50% A/50 % B (A = 400/300/300/0.8 v/v DI H<sub>2</sub>O/Acetonitrile/2-Propanol/Phosphoric Acid and B = 2-Propanol), followed by a 5 minute hold at this condition and a 10 minute

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gradient to the initial condition. The detection method was UV absorbance at 210 nm.

The results of the equilibrium solubility studies are given in Tables 13a-13c.

5

Table 13a. Equilibrium Solubilities of Compound A in Triglyceride/ surfactant(s)

Vehicle	Solubility (mgA/ml)
	Cmpd A
Miglyol® 812/Capmul® MCM (80/20)	74
Miglyol® 812/Capmul® MCM/Polysorbate 80 (40/40/20)	58
Miglyol® 812/Capmul® MCM/Polysorbate 80 (20/60/20)	63
Miglyol® 812/Tagat® TO (80/20)	58
Miglyol® 812/Labrafil® M 1944 (80/20)	59
Miglyol® 812/Labrafil® M 2125 (80/20)	57
Miglyol® 812/Labrasol® (80/20)	69
Miglyol® 812/Cremophor® EL 80/20	68
Olive oil/Capmul® MCM (80/20)	23

10

Table 13b. Equilibrium Solubility of Compound A in Triglyceride/solvent

Vehicle	Solubility (mgA/ml)
Miglyol® 812/triacetin (90/10)*	106
Miglyol® 812/Peppermint oil (90/10)	79
Miglyol® 812/Peppermint oil (80/20)	93
Olive oil /Peppermint oil (90/10)	25

15 \* Not completely miscible

20

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Table 13c. Equilibrium Solubility of Compound A in Miglyol/Solvent/surfactant

Vehicle	Solubility (mgA/ml)
Miglyol <sup>®</sup> 812/Propylene carbonate/Cremophor <sup>®</sup> EL	
72/8/20	108
60/20/20	146
55/25/20	158
40/40/20	209
30/50/20	228
Miglyol <sup>®</sup> 812/Ethyl lactate/Cremophor <sup>®</sup> EL	
72/8/20	94
70/10/20	99
65/15/20	120
60/20/20	143
50/30/20	196
40/40/20	221
30/50/20	256
Miglyol <sup>®</sup> 812/Triacetin/Cremophor <sup>®</sup> EL	
72/8/20	94
65/15/20	111
60/20/20	133
50/30/20	158
40/40/20	183
30/50/20	198
Miglyol <sup>®</sup> 812/Peppermint Oil/Cremophor <sup>®</sup> EL (72/8/20)	72
Miglyol <sup>®</sup> 812/EtOH/Cremophor <sup>®</sup> EL (76/4/20)	89
Miglyol <sup>®</sup> 812/Ethyl lactate/Tagat <sup>®</sup> TO (72/8/20)	87
Miglyol <sup>®</sup> 812/Ethyl lactate/Labrasol <sup>®</sup> (72/8/20)	98
Miglyol <sup>®</sup> 812/Propylene carbonate/Tagat <sup>®</sup> TO (72/8/20)	111
Miglyol <sup>®</sup> 812/Propylene carbonate/Labrasol <sup>®</sup> (72/8/20)	116

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**Example 14:**

- 5 For CETP inhibitors where quantities were limited or the samples were amorphous solids, an estimate of solubility was obtained by addition of vehicle to a known quantity of the compound and mixing in an ultrasonicator bath for 90 minutes, followed by overnight equilibration at ambient temperature. Addition of vehicle was repeated until a solution was achieved. From the total volume of vehicle added to
- 10 solubilize the CETP inhibitor compound, the solubility value, or so-called microsolubility, was calculated by the equation:

$$\text{Weight of sample (mgA) / vehicle volume (mL) = Microsolubility (mgA/mL)}$$

- 15 The microsolubility values for CETP inhibitors in various vehicles are given in Tables 14a – 14c.

Table 14a. Microsolubility Data for Crystalline Compounds

20

Solvent	Solubility (mg/mL)	
	Cmpd A	Cmpd B
Crodamol® GTCC	< 75	<20
Miglyol® 810	< 100	
Long chain triglycerides (soy, peanut, corn, safflower, sesame)	<75	<100
Cotton oil	<75	
Olive oil		<100
Capmul® MCM		<100
PEG 400		<100
Crodamol® GTCC /Capmul® MCM/ Polysorbate 80 (40/40/20)		<100
Linoleic acid	< 60	
Incromega® TG2671	<75	
propylene glycol	< 75	
Glycerin	< 75	
mineral oil	<75	

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Table 14b. Microsolubilities of amorphous compounds (mg/mL)

	Cmpd F	Cmpd G	Cmpd H	Cmpd I	Cmpd J
Miglyol <sup>®</sup> 812	<100				
Crodamol <sup>®</sup> GTCC			>300	>20	>100
Corn, Safflower, Soybean oils			>300	<20	>100
Peanut oil				<20	>100
Olive oil	303	>300	>300	<20	>100
Sesame oil		>300		<20	>100
Cremophor <sup>®</sup> EL		>300	<160		
Capmul <sup>®</sup> MCM			>300	>20	>100
PEG 400			<160	<20	50-100
Corn oil/Polysorbate 80 (80/20)				>20	
Corn oil/Labrafil (80/20)				<20	
Crodamol <sup>®</sup> GTCC /Capmul <sup>®</sup> MCM/ Polysorbate 80 (40/40/20)		>300		>20	>100

5 Table 14c. Microsolubilities of amorphous compounds (mg/mL)

	Olive oil	Safflower oil	Miglyol <sup>®</sup> 812	Capmul <sup>®</sup> MCM
Cmpd L	<300	>300	>300	>300
Cmpd M	<300	<300	>300	>300
Cmpd A	>300	>300	>300	>300
Cmpd N	>300	>300	>300	>300
Cmpd O	<300	<300	>300	>300
Cmpd P	>300	<300	>300	>300
Cmpd Q	<300	<300	>300	>300

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**Example 15:**

To 1.41 mL of Miglyol<sup>®</sup> 812, 0.471 mL of propylene carbonate and 0.471 mL of Cremophor<sup>®</sup> EL was added 900 mg of Compound E. The resulting mixture was stirred at ambient temperature for 20 minutes with scraping of the container walls as needed. It was then probe sonicated for 30 seconds with occasional mixing to completely dissolve the drug, and then stirred for 20 minutes at ambient temperature. The amounts (in mg) of each component in the oil solution per gram of solution are set forth in Table 15.

Table 15

Ingredient	mg/g
Compound E	275
Miglyol <sup>®</sup> 812	406
Propylene carbonate	166
Cremophor <sup>®</sup> EL	153

An emulsion was prepared by combining 1 volume of oil solution with an equal volume of de-ionized water. This mixture was stirred for 10 minutes and then vortex mixed for 1 minute to yield an emulsion with an average particle size less than 10 microns. The emulsion is then stirred continuously to maintain homogeneity. No chemical degradation based on HPLC analysis or crystallization based on microscopic examination was detected in the oil or emulsion after storage for 24 hr.

**Example 16:**

Capmul<sup>®</sup> MCM was heated to 55°C and mixed. Cremophor<sup>®</sup> RH40 was also heated to 65°C with stirring. Then 2.70 g of triacetin, 2.71 g of Cremophor<sup>®</sup> RH40, and 3.60 g of Capmul<sup>®</sup> MCM were combined and mixed for 20 min. To this mixture was then added 1.01 gm of Compound A and the resulting mixture stirred at ambient temperature for 3 hours with scraping of walls as needed. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 16a.

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Table 16a

Ingredient	mg/g
Cmpd A	100
Triacetin	270
Cremophor® RH40	270
Capmul® MCM	360

5

**Example 17:**

To 495 mg of Miglyol® 812, 203 mg of propylene carbonate and 187 mg of Cremophor® EL was added 115 mg of Compound A. The resulting mixture was stirred at ambient temperature for 20 minutes with scraping of the container walls as needed. It was then probe sonicated for 3 minutes with occasional mixing to completely dissolve the drug, and then stirred for 20 minutes at ambient temperature. The amounts (in mg) of each component in the oil solution per gram of solution are set forth in Table 17a.

10  
15

Table 17a

Ingredient	mg/g
Cmpd A	115
Miglyol® 812	495
Propylene carbonate	203
Cremophor® EL	187

An emulsion was prepared by combining 1 volume of oil solution with an equal volume of de-ionized water. This mixture was stirred for 10 minutes and then vortex mixed for 2 minutes. The emulsion had an average particle size of less than 10 microns. It was stirred continuously to maintain homogeneity. No chemical degradation based on HPLC analysis or crystallization based on microscopic examination was detected in the oil after storage for 8 days or the emulsion after storage for 24 hr.

20  
25

**Example 18:**

- To 764 mg of olive oil and 223 mg of Cremophor<sup>®</sup> EL was added 13 mg of Compound A. The resulting mixture was stirred at ambient temperature for 20 minutes with scraping of container walls as needed. It was then probe sonicated for 3 minutes with occasional mixing to completely dissolve the drug. The solution was then stirred for 20 minutes at ambient temperature. The amounts (in mg) of each component in the oil solution per gram of solution are set forth in Table 18a.

10

Table 18a

Ingredient	mg/g
Compound A	13
Olive oil	764
Cremophor <sup>®</sup> EL	223

- 15 An emulsion was prepared by combining combining 1 volume of oil solution with an equal volume of de-ionized water. This mixture was stirred for 10 minutes and then vortex mixed for 2 minutes. The emulsion had an average particle size of less than 10 microns. It was stirred continuously to maintain homogeneity. No chemical degradation based on HPLC analysis or crystallization based on microscopic examination was detected in the oil after storage for 8 days or the emulsion after storage for 24 hr.

20

**Example 19:**

- 25 To 485 mg of Miglyol<sup>®</sup> 812, 199 mg of propylene carbonate and 183 mg of Cremophor<sup>®</sup> EL was added 133 mg of Compound D. The resulting mixture was stirred at ambient temperature for 20 minutes with scraping of container walls as needed. It was then probe sonicated for 3 minutes with occasional mixing to completely dissolve the drug. The solution was stirred for further stirred for 20 minutes at ambient temperature. The amounts (in mg) of each component in the oil solution per gram of solution are set forth in Table 19A.

30



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Table 19A

Ingredient	mg/g
Cmpd D	133
Miglyol® 812	485
Propylene carbonate	199
Cremophor® EL	183

An emulsion was prepared by combining combining 1 volume of oil solution with an equal volume of de-ionized water. This mixture was stirred for 10 minutes and then  
5 vortex mixed for 2 minutes. The emulsion had an average particle size of less than 10 microns. It was stirred continuously to maintain homogeneity. No chemical degradation based on HPLC analysis or crystallization based on microscopic examination was detected in the oil after storage for 8 days or the emulsion after storage for 24 hr.

10

**Example 20:**

Chemical and physical stability for the formulation of Example 8 was determined for 30 mgA Miglyol® (#11 oblong) softgels stored in white HPDE bottles (child-resistant closures). After storage at 40°C/75%RH for 6 months there was no change in potency  
15 and no degradation was detected (peak area < 0.05 % relative to parent) as determined by HPLC analysis of the entire softgel. The appearance (color, shape, seal integrity) was unchanged, and disintegration occurred within 15 minutes in water (USP<701>). Softgels stored at 5°C and 25°C/60% RH were stable for 18 months.

20 **Example 21:**

Either oils or preformed emulsions of Compound A were administered to Sprague Dawley rats by oral gavage and the results are shown in Table 21a. Emulsions were prepared as indicated in Examples 17-19. Emulsions prepared from olive oil/surfactant provided the best results. The solubility and thus the accessible dose  
25 could be increased by using cosolvents (e.g. caprylic acid and/or triacetin) or using a triglyceride with improved solubility (Miglyol® 812), but this did not provide any improvement in exposure over much lower doses in olive oil/Cremophor® EL. Administration of pre-formed emulsions gave superior results to the oil, especially at higher dose volumes where mixing of phases in vivo may be less efficient.

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In contrast to the results in rats, emulsions in Miglyol® 812/Cremophor® EL yielded far superior results to olive oil/Cremophor® EL in cynomolgous monkeys (Table 21b), and much better results than for Miglyol® alone. Use of an emulsion prepared from crystalline (ethanolate) drug allowed comparable exposures to be achieved to those for more soluble amorphous drug in Miglyol® alone. Excellent dose proportionality was also obtained.

The need for the presence of a high concentration of the long chain triglyceride olive oil for efficient absorption in the rat, but not the monkey, suggests that the lymphatic pathway plays a more important role for absorption of this drug in rats. An important role for lymphatic absorption for Compound A is consistent with its very high lipophilicity.

Table 21a. PK results in rat for Compound A

Drug Form	Vehicle	Dose (mg/kg)	Conc. in oil (mg/mL)	Vol. of oil (mg/kg)	Cmax (µg/mL)	AUC (0-Tlast) (µg-hr/mL)
Ethanol.	Olive oil/ Cremophor® / water 40/10/50	100	20	5	6.2	33*
Ethanol.	Miglyol® /Cremophor® /water 40/10/50	500	100	5	4.6	18*
Ethanol.	Olive oil/caprylic acid/ Cremophor®/water 10/30/10/50	375	75	5	4.1	21*
Ethanol.	Olive oil/caprylic acid/triacetin/ Cremophor®/water 10/15/15/10/50	625	125	5	4.8	26*
Ethanol.	Olive oil/ Cremophor® 80/20	100	20	5	3.6	45
Ethanol.	Miglyol® / Cremophor® / water 40/10/50	100	100	1	1.9	23
Ethanol.	Miglyol®/Cremophor®/ 0.5 % HPMCAS 40/10/50	100	100	1	1.6	15
Ethanol.	Miglyol®	500	100	5	2.1	27
Amorph.	Olive oil	300	60	5	7.3	50

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\* Tlast = 9 hr. Otherwise, Tlast = 24 hr.

Amorph. = amorphous anhydrous

Ethanol. = crystalline ethanolate

5 HPMCAS=Hydroxypropyl methyl cellulose acetate succinate

Table 21b. PK results in monkeys for Compound A

Form*	Vehicle	Dose (mg /kg)	Conc. in oil (mg/mL)	Vol. of oil (mg/kg)	Cmax (µg/mL)	AUC (µg-hr/mL)
Ethanol.	Miglyol <sup>®</sup> / Cremophor <sup>®</sup> / water 40/10/50	100 (BID)	100	1	1.6-2.3	24-29
Ethanol.	Miglyol <sup>®</sup> / Cremophor <sup>®</sup> / water 40/10/50	50 (BID)	50	1	0.8 - 1.1	13-15
Ethanol.	Miglyol <sup>®</sup> / Cremophor <sup>®</sup> / water 40/10/50	100	100	1	0.4-1.8	
Ethanol.	Olive oil/ Cremophor <sup>®</sup> / water 40/10/50	20	20	1	0.1, 0.16	N.D.
Ethanol.	Miglyol <sup>®</sup>	100	100	1	ca. 0.17	N.D.
Amorph.	Miglyol <sup>®</sup>	100	100	1	ca. 1.6	ca. 29

\* Amorph. = amorphous anhydrous

Ethanol. = crystalline ethanolate

### Example 22:

#### A. 100 mgA/mL fill

Capmul<sup>®</sup> MCM was heated to 55°C and mixed. Then 48.5 gm of Miglyol<sup>®</sup> 812, 72.8

gm of triacetin, 48.5 gm of Polysorbate 80, and 72.8 gm of Capmul<sup>®</sup> MCM were combined. To this mixture was then added 25.0 gm Compound E and the resulting mixture stirred at ambient temperature for 10 minutes with scraping of walls as

needed. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 22. The fill could be prepared on a larger scale for encapsulation into

#10 oval softgels to provide a fill volume of 0.6 mL and a dose per softgel of 60 mgA.

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## B. 200 mgA/mL fill

Capmul® MCM was heated to 55°C and mixed. Then 650 mg of Miglyol® 812, 976 mg of triacetin, 650 mg of Polysorbate 80, and 976 mg of Capmul® MCM were combined and mixed for 10 min. To this mixture was then added 748 mg Compound E and the  
5 resulting mixture stirred at ambient temperature for 10 minutes with scraping of wall as needed. The amounts (in mg) of each component in the fill per gram of fill are set forth in Table 22. The fill could be prepared on a larger scale for encapsulation into #10 oval softgels to provide a fill volume of 0.6 mL and a dose per softgel of 120 mgA.

10 Table 22

Ingredient	mg/g	
	100 mgA/mL	200 mgA/mL
Compound E	94	184
Miglyol® 812	181	163
Triacetin	272	245
Polysorbate 80	181	163
Capmul® MCM	272	245

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What is claimed is:

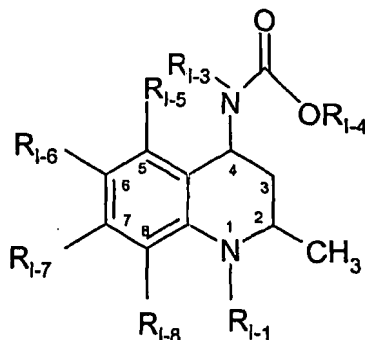
1. A composition comprising a CETP inhibitor and a lipophilic vehicle selected from digestible oils, lipophilic solvents, surfactants, and mixtures of any two or more thereof.
2. A composition, comprising  
a CETP inhibitor;  
a co-solvent;  
a high HLB surfactant;  
a low HLB surfactant; and  
optionally, a digestible oil.
3. A composition as defined in claim 2, wherein said CETP inhibitor has an aqueous solubility less than 10 µg/mL.
4. A composition as defined in claim 2, wherein said co-solvent is selected from triacetin, propylene carbonate, transcutool, ethyl lactate, triethyl citrate, N-methyl-2-pyrrolidone, dimethylisosorbide and glycofurool.
5. A composition as defined in claim 2, wherein said (high HLB) hydrophilic surfactant is selected from polyoxyethylene 20 sorbitan monooleate (polysorbate 80), polyoxyethylene 20 sorbitan monolaurate, polyethylene (40 or 60) hydrogenated castor oil, polyoxyethylene (35) castor oil, alpha tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS), glyceryl PEG 8 caprylate/caprate, PEG 32 glyceryl laurate, polyoxyethylene fatty acid esters, and polyoxyethylene fatty acid ethers.
6. A composition as defined in claim 2, wherein said (low HLB) lipophilic surfactant is selected from mono and diglycerides of capric and caprylic acid, polyoxyethylene 6 apricot kernel oil, polyoxyethylene corn oil, propylene glycol monolaurate, propylene glycol dicaprylate/caprate, polyglyceryl oleate, sorbitan esters of fatty acids, and glyceryl monooleate.
7. A composition as defined in claim 2, which is self-emulsifying and comprises the following amounts of components:  
1-50 % CETP inhibitor;  
5 – 60 % cosolvent;  
5 - 75 % high HLB surfactant; and  
5 – 75 % low HLB surfactant.

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8. A composition as defined in claim 1, wherein said CETP inhibitor is selected from any of the following classes:

(1) an oxy substituted 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinoline having the Formula I

5



Formula I

10 or a pharmaceutically acceptable salt, enantiomer, or stereoisomer of said compound;

wherein  $R_{I-1}$  is hydrogen,  $Y_1$ ,  $W_1-X_1$ ,  $W_1-Y_1$ ;

wherein  $W_1$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

$X_1$  is  $-O-Y_1$ ,  $-S-Y_1$ ,  $-N(H)-Y_1$  or  $-N-(Y_1)_2$ ;

15 wherein  $Y_1$  for each occurrence is independently  $Z_1$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is  
20 optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $Z_1$ ;

25 wherein  $Z_1$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

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- wherein said Z<sub>1</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-,
- 5 di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;
- R<sub>1-3</sub> is hydrogen or Q<sub>i</sub>;
- 10 wherein Q<sub>i</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-
- 15 substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>i</sub>;
- wherein V<sub>i</sub> is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected
- 20 independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;
- wherein said V<sub>i</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted
- 25 independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carbamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-
- 30 C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituents are also optionally substituted with from one to nine fluorines;
- R<sub>1-4</sub> is Q<sub>i-1</sub> or V<sub>i-1</sub>

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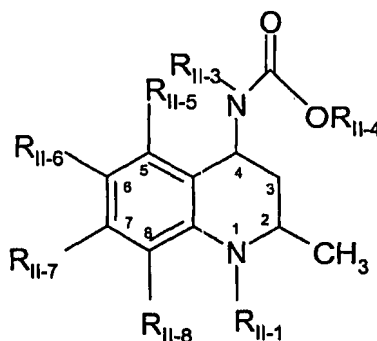
- wherein  $Q_{1-1}$  is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{1-1}$ ;
- 10 wherein  $V_{1-1}$  is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;
- wherein said  $V_{1-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;
- 15 wherein either  $R_{1-3}$  must contain  $V_1$  or  $R_{1-4}$  must contain  $V_{1-1}$ ; and  $R_{1-5}$ ,  $R_{1-6}$ ,  $R_{1-7}$  and  $R_{1-8}$  are each independently hydrogen, hydroxy or oxy wherein
- 20 said oxy is substituted with  $T_1$  or a partially saturated, fully saturated or fully unsaturated one to twelve membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon
- 25 is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $T_i$ ;
- wherein  $T_1$  is a partially saturated, fully saturated or fully unsaturated three to
- 30 eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;



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wherein said T<sub>1</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

(2) a 4-carboxyamino-2-methyl-1,2,3,4,-tetrahydroquinoline, having the  
Formula II



Formula II

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or a pharmaceutically acceptable salt, enantiomer, or stereoisomer of said compound;

wherein R<sub>II-1</sub> is hydrogen, Y<sub>II</sub>, W<sub>II</sub>-X<sub>II</sub>, W<sub>II</sub>-Y<sub>II</sub>;

wherein W<sub>II</sub> is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

20 X<sub>II</sub> is -O-Y<sub>II</sub>, -S-Y<sub>II</sub>, -N(H)-Y<sub>II</sub> or -N-(Y<sub>II</sub>)<sub>2</sub>;

wherein Y<sub>II</sub> for each occurrence is independently Z<sub>II</sub> or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted

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with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z<sub>II</sub>;

5 Z<sub>II</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

10 wherein said Z<sub>II</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl is also optionally substituted with from one to nine fluorines;

R<sub>II-3</sub> is hydrogen or Q<sub>II</sub>;

20 wherein Q<sub>II</sub> is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>II</sub>;

25 wherein V<sub>II</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

30 wherein said V<sub>II</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)

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- alkylcarboxamoyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino or said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituents are optionally substituted with from one to nine fluorines;
- 5 R<sub>II-4</sub> is Q<sub>II-1</sub> or V<sub>II-1</sub>
- wherein Q<sub>II-1</sub> a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo,
- 10 and said carbon chain is optionally mono-substituted with V<sub>II-1</sub>;
- wherein V<sub>II-1</sub> is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;
- wherein said V<sub>II-1</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, nitro, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-substituted with oxo, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally substituted with from one to nine fluorines;
- 20 wherein either R<sub>II-3</sub> must contain V<sub>II</sub> or R<sub>II-4</sub> must contain V<sub>II-1</sub>; and
- 25 R<sub>II-5</sub>, R<sub>II-6</sub>, R<sub>II-7</sub> and R<sub>II-8</sub> are each independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T<sub>II</sub> or a partially saturated, fully saturated or fully unsaturated (C<sub>1</sub>-C<sub>12</sub>) straight or branched carbon chain wherein carbon may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon is optionally mono-substituted with T<sub>II</sub>;
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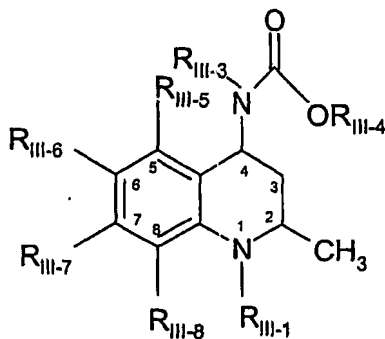
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wherein  $T_{II}$  is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $T_{II}$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

provided that at least one of substituents  $R_{II-5}$ ,  $R_{II-6}$ ,  $R_{II-7}$  and  $R_{II-8}$  is not hydrogen and is not linked to the quinoline moiety through oxy;

(3) an annulated 4-carboxyamino-2-methyl-1,2,3,4,-tetrahydroquinoline having the Formula III



Formula III

or a pharmaceutically acceptable salt, enantiomer, or stereoisomer of said compound;

wherein  $R_{III-1}$  is hydrogen,  $Y_{III}$ ,  $W_{III}-X_{III}$ ,  $W_{III}-Y_{III}$ ;

wherein  $W_{III}$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

$X_{III}$  is  $-O-Y_{III}$ ,  $-S-Y_{III}$ ,  $-N(H)-Y_{III}$  or  $-N-(Y_{III})_2$ ;

- Y<sub>III</sub> for each occurrence is independently Z<sub>III</sub> or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z<sub>III</sub>;
- 10 wherein Z<sub>III</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected
- 15 independently from nitrogen, sulfur and oxygen;
- wherein said Z<sub>III</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-,
- 20 di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to nine fluorines; R<sub>III-3</sub> is hydrogen or Q<sub>III</sub>;
- wherein Q<sub>III</sub> is a fully saturated, partially unsaturated or fully unsaturated one
- 25 to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally
- 30 mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>III</sub>;
- wherein V<sub>III</sub> is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

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fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $V_{III}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino or said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl are optionally substituted with from one to nine fluorines;

$R_{III-4}$  is  $Q_{III-1}$  or  $V_{III-1}$ ;

wherein  $Q_{III-1}$  a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{III-1}$ ;

wherein  $V_{III-1}$  is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said  $V_{III-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent optionally having from one to nine fluorines;

wherein either  $R_{III-3}$  must contain  $V_{III}$  or  $R_{III-4}$  must contain  $V_{III-1}$ ; and  $R_{III-5}$  and  $R_{III-6}$ , or  $R_{III-6}$  and  $R_{III-7}$ , and/or  $R_{III-7}$  and  $R_{III-8}$  are taken together and form at least one four to eight membered ring that is partially saturated or fully unsaturated

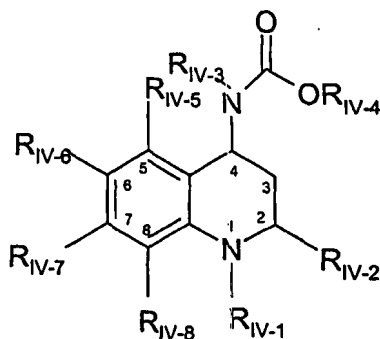
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optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by R<sub>III-5</sub> and R<sub>III-6</sub>, or R<sub>III-6</sub> and R<sub>III-7</sub>, and/or R<sub>III-7</sub> and R<sub>III-8</sub> are optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent optionally having from one to nine fluorines;

provided that the R<sub>III-5</sub>, R<sub>III-6</sub>, R<sub>III-7</sub> and/or R<sub>III-8</sub>, as the case may be, that do not form at least one ring are each independently hydrogen, halo, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl, said (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally having from one to nine fluorines;

(4) a 4-carboxyamino-2-substituted-1,2,3,4,-tetrahydroquinoline, having the Formula IV



Formula IV

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

wherein R<sub>IV-1</sub> is hydrogen, Y<sub>IV</sub>, W<sub>IV</sub>-X<sub>IV</sub> or W<sub>IV</sub>-Y<sub>IV</sub>;

wherein W<sub>IV</sub> is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

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$X_{IV}$  is -O- $Y_{IV}$ , -S- $Y_{IV}$ , -N(H)- $Y_{IV}$  or -N-( $Y_{IV}$ )<sub>2</sub>;

wherein  $Y_{IV}$  for each occurrence is independently  $Z_{IV}$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally  
 5 be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said  
 10 carbon chain is optionally mono-substituted with  $Z_{IV}$ ;

wherein  $Z_{IV}$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered  
 15 rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $Z_{IV}$  substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or  
 20 di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, amino, nitro, cyano, oxo, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

$R_{IV-2}$  is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is  
 25 optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo; or said  $R_{IV-2}$  is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to  
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two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein said  $R_{IV-2}$  ring is optionally attached through  $(C_1-C_4)$ alkyl;

wherein said  $R_{IV-2}$  ring is optionally mono-, di- or tri-substituted independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, oxo or  $(C_1-C_6)$ alkyloxycarbonyl;

with the proviso that  $R_{IV-2}$  is not methyl;

10  $R_{IV-3}$  is hydrogen or  $Q_{IV}$ ;

wherein  $Q_{IV}$  is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{IV}$ ;

20 wherein  $V_{IV}$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

25 wherein said  $V_{IV}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituents are also optionally substituted with from one to nine fluorines;

$R_{IV-4}$  is  $Q_{IV-1}$  or  $V_{IV-1}$ ;

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wherein  $Q_{IV-1}$  a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $V_{IV-1}$ ;

10 wherein  $V_{IV-1}$  is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said  $V_{IV-1}$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, amino, nitro, cyano,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-substituted with oxo, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein either  $R_{IV-3}$  must contain  $V_{IV}$  or  $R_{IV-4}$  must contain  $V_{IV-1}$ ;  
 $R_{IV-5}$ ,  $R_{IV-6}$ ,  $R_{IV-7}$  and  $R_{IV-8}$  are each independently hydrogen, a bond, nitro or halo  
20 wherein said bond is substituted with  $T_{IV}$  or a partially saturated, fully saturated or fully unsaturated  $(C_1-C_{12})$  straight or branched carbon chain wherein carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon is optionally mono-substituted with  $T_{IV}$ ;

wherein  $T_{IV}$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected  
30 independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

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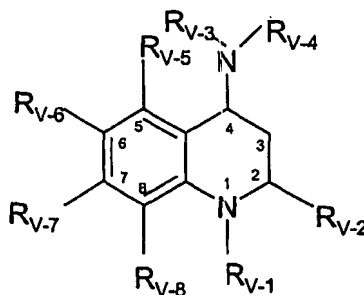
wherein said  $T_{IV}$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-,  
 5 di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines; and

wherein  $R_{IV-5}$  and  $R_{IV-6}$ , or  $R_{IV-6}$  and  $R_{IV-7}$ , and/or  $R_{IV-7}$  and  $R_{IV-8}$  may also be  
 10 taken together and can form at least one four to eight membered ring that is partially saturated or fully unsaturated optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by  $R_{IV-5}$  and  $R_{IV-6}$ , or  $R_{IV-6}$  and  $R_{IV-7}$ , and/or  $R_{IV-7}$  and  $R_{IV-8}$  are optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_4)$ alkylsulfonyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio,  
 15 amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino,  
 20 said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

with the proviso that when  $R_{IV-2}$  is carboxyl or  $(C_1-C_4)$ alkylcarboxyl, then  $R_{IV-1}$  is not hydrogen;

(5) a 4-amino substituted-2-substituted-1,2,3,4,-tetrahydroquinoline, having the  
 25 Formula V



Formula V

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or a pharmaceutically acceptable salt, enantiomer, or stereoisomers of said compound;

wherein  $R_{V-1}$  is  $Y_V$ ,  $W_V-X_V$  or  $W_V-Y_V$ ;

wherein  $W_V$  is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

5  $X_V$  is  $-O-Y_V$ ,  $-S-Y_V$ ,  $-N(H)-Y_V$  or  $-N-(Y_V)_2$ ;

wherein  $Y_V$  for each occurrence is independently  $Z_V$  or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur  
10 and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $Z_V$ ;

15 wherein  $Z_V$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected  
20 independently from nitrogen, sulfur and oxygen;

wherein said  $Z_V$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-,  
25 di- or tri-substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent is also optionally substituted with from one to nine fluorines;

$R_{V-2}$  is a partially saturated, fully saturated or fully unsaturated one to six  
30 membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with

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hydroxy, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo; or said  $R_{V-2}$  is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein

5 said  $R_{V-2}$  ring is optionally attached through  $(C_1-C_4)$ alkyl;

wherein said  $R_{V-2}$  ring is optionally mono-, di- or tri-substituted independently with halo,  $(C_2-C_6)$ alkenyl,  $(C_1-C_6)$  alkyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-

10 substituted independently with halo, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, oxo or  $(C_1-C_6)$ alkyloxycarbonyl;

$R_{V-3}$  is hydrogen or  $Q_V$ ;

wherein  $Q_V$  is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than

15 the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted

20 with oxo, and said carbon chain is optionally mono-substituted with  $V_V$ ;

wherein  $V_V$  is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered

25 rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said  $V_V$  substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N- $(C_1-C_6)$

30 alkylcarboxamoyl, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or

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di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, said (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>2</sub>-C<sub>6</sub>)alkenyl substituents are also optionally substituted with from one to nine fluorines;

R<sub>V-4</sub> is cyano, formyl, W<sub>V-1</sub>Q<sub>V-1</sub>, W<sub>V-1</sub>V<sub>V-1</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkyleneV<sub>V-1</sub> or V<sub>V-2</sub>;

wherein W<sub>V-1</sub> is carbonyl, thiocarbonyl, SO or SO<sub>2</sub>,

5        wherein Q<sub>V-1</sub> a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is  
10        optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V<sub>V-1</sub>;

wherein V<sub>V-1</sub> is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected

15        independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V<sub>V-1</sub> substituent is optionally mono-, di-, tri-, or tetra-substituted  
20        independently with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkylamino wherein said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is optionally mono-substituted with oxo, said (C<sub>1</sub>-C<sub>6</sub>)alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein V<sub>V-2</sub> is a partially saturated, fully saturated or fully unsaturated five to  
25        seven membered ring containing one to four heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V<sub>V-2</sub> substituent is optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>2</sub>)alkyl, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, hydroxy, or oxo wherein said (C<sub>1</sub>-C<sub>2</sub>)alkyl optionally has from one to five fluorines; and

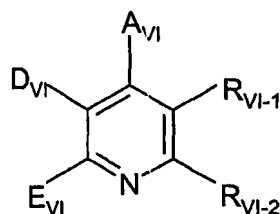
30        wherein R<sub>V-4</sub> does not include oxycarbonyl linked directly to the C<sup>4</sup> nitrogen; wherein either R<sub>V-3</sub> must contain V<sub>V</sub> or R<sub>V-4</sub> must contain V<sub>V-1</sub>;

R<sub>V-5</sub>, R<sub>V-6</sub>, R<sub>V-7</sub> and R<sub>V-8</sub> are independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T<sub>V</sub> or a partially saturated, fully saturated or fully unsaturated (C<sub>1</sub>-C<sub>12</sub>) straight or branched carbon chain wherein carbon may

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- optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is
- 5 optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with  $T_V$ ;
- wherein  $T_V$  is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two
- 10 fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;
- wherein said  $T_V$  substituent is optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-,
- 15 di- or tri-substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent also optionally has from one to nine
- 20 fluorines;
- wherein  $R_{V-5}$  and  $R_{V-6}$ , or  $R_{V-6}$  and  $R_{V-7}$ , and/or  $R_{V-7}$  and  $R_{V-8}$  may also be taken together and can form at least one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;
- 25 wherein said rings formed by  $R_{V-5}$  and  $R_{V-6}$ , or  $R_{V-6}$  and  $R_{V-7}$ , and/or  $R_{V-7}$  and  $R_{V-8}$  are optionally mono-, di- or tri-substituted independently with halo,  $(C_1-C_6)$ alkyl,  $(C_1-C_4)$ alkylsulfonyl,  $(C_2-C_6)$ alkenyl, hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino wherein said  $(C_1-C_6)$ alkyl substituent is optionally mono-, di- or tri-
- 30 substituted independently with hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_4)$ alkylthio, amino, nitro, cyano, oxo, carboxy,  $(C_1-C_6)$ alkyloxycarbonyl, mono-N- or di-N,N- $(C_1-C_6)$ alkylamino, said  $(C_1-C_6)$ alkyl substituent also optionally has from one to nine fluorines;
- (6) a cycloalkano-pyridine having the Formula VI

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Formula VI

or a pharmaceutically acceptable salt, enantiomer, or stereoisomer of said compounds;

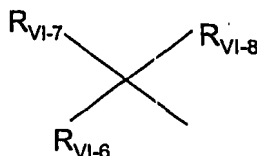
5 in which

$A_{VI}$  denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with up to five identical or different substituents in the form of a halogen, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy or a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy containing up to 7 carbon atoms each, or in the form of a group according to the formula  $-BNR_{VI-3}R_{VI-4}$ , wherein

$R_{VI-3}$  and  $R_{VI-4}$  are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms,

$D_{VI}$  denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with a phenyl, nitro, halogen, trifluoromethyl or trifluoromethoxy, or a

15 radical according to the formula  $R_{VI-5}-L_{VI-1}$ ,



or  $R_{VI-9}-T_{VI}-V_{VI}-X_{VI}$ , wherein

20  $R_{VI-5}$ ,  $R_{VI-6}$  and  $R_{VI-9}$  denote, independently from one another, a cycloalkyl containing 3 to 6 carbon atoms, or an aryl containing 6 to 10 carbon atom or a 5- to 7-membered, optionally benzo-condensed, saturated or unsaturated, mono-, bi- or tricyclic heterocycle containing up to 4 heteroatoms from the series of S, N and/or O, wherein the rings are optionally substituted, in the case of the nitrogen-containing

25 rings also via the N function; with up to five identical or different substituents in the form of a halogen, trifluoromethyl, nitro, hydroxyl, cyano, carboxyl, trifluoromethoxy, a straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl containing up to 6 carbon atoms each, an aryl or trifluoromethyl-



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substituted aryl containing 6 to 10 carbon atoms each, or an optionally benzo-condensed, aromatic 5- to 7-membered heterocycle containing up to 3 heteroatoms from the series of S, N and/or O, and/or in the form of a group according to the formula  $\text{BOR}_{\text{VI}-10}$ ,  $-\text{SR}_{\text{VI}-11}$ ,  $-\text{SO}_2\text{R}_{\text{VI}-12}$  or  $\text{BNR}_{\text{VI}-13}\text{R}_{\text{VI}-14}$ , wherein

- 5  $\text{R}_{\text{VI}-10}$ ,  $\text{R}_{\text{VI}-11}$  and  $\text{R}_{\text{VI}-12}$  denote, independently from one another, an aryl containing 6 to 10 carbon atoms, which is in turn substituted with up to two identical or different substituents in the form of a phenyl, halogen or a straight-chain or branched alkyl containing up to 6 carbon atoms,

$\text{R}_{\text{VI}-13}$  and  $\text{R}_{\text{VI}-14}$  are identical or different and have the meaning of  $\text{R}_{\text{VI}-3}$  and

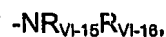
- 10  $\text{R}_{\text{VI}-4}$  given above, or

$\text{R}_{\text{VI}-5}$  and/or  $\text{R}_{\text{VI}-6}$  denote a radical according to the formula



$\text{R}_{\text{VI}-7}$  denotes a hydrogen or halogen, and

- 15  $\text{R}_{\text{VI}-8}$  denotes a hydrogen, halogen, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, a straight-chain or branched alkoxy or alkyl containing up to 6 carbon atoms each, or a radical according to the formula



wherein

$\text{R}_{\text{VI}-15}$  and  $\text{R}_{\text{VI}-16}$  are identical or different and have the meaning of  $\text{R}_{\text{VI}-3}$  and

- 20  $\text{R}_{\text{VI}-4}$  given above, or

$\text{R}_{\text{VI}-7}$  and  $\text{R}_{\text{VI}-8}$  together form a radical according to the formula  $=\text{O}$  or  $=\text{NR}_{\text{VI}-17}$ ,

wherein

$\text{R}_{\text{VI}-17}$  denotes a hydrogen or a straight-chain or branched alkyl, alkoxy or acyl containing up to 6 carbon atoms each,

- 25  $\text{L}_{\text{VI}}$  denotes a straight-chain or branched alkylene or alkenylene chain containing up to 8 carbon atoms each, which are optionally substituted with up to two hydroxyl groups,

$\text{T}_{\text{VI}}$  and  $\text{X}_{\text{VI}}$  are identical or different and denote a straight-chain or branched alkylene chain containing up to 8 carbon atoms, or

- 30  $\text{T}_{\text{VI}}$  or  $\text{X}_{\text{VI}}$  denotes a bond,

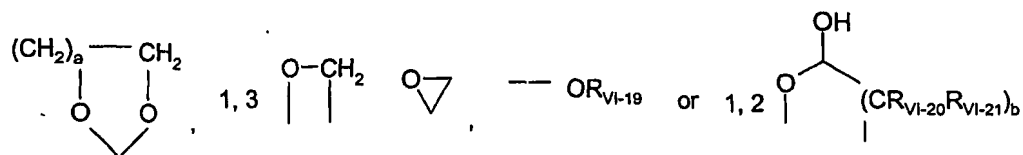
$\text{V}_{\text{VI}}$  denotes an oxygen or sulfur atom or an  $\text{BNR}_{\text{VI}-18}$  group, wherein

$\text{R}_{\text{VI}-18}$  denotes a hydrogen or a straight-chain or branched alkyl containing up to 6 carbon atoms or a phenyl,

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$E_{VI}$  denotes a cycloalkyl containing 3 to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally substituted with a cycloalkyl containing 3 to 8 carbon atoms or a hydroxyl, or a phenyl, which is optionally substituted with a halogen or trifluoromethyl,

- 5  $R_{VI-1}$  and  $R_{VI-2}$  together form a straight-chain or branched alkylene chain containing up to 7 carbon atoms, which must be substituted with a carbonyl group and/or a radical according to the formula



- 10 wherein

a and b are identical or different and denote a number equaling 1, 2 or 3,

- 15  $R_{VI-19}$  denotes a hydrogen atom, a cycloalkyl containing 3 to 7 carbon atoms, a straight-chain or branched silylalkyl containing up to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally substituted with a hydroxyl, a straight-chain or a branched alkoxy containing up to 6 carbon atoms or a phenyl, which may in turn be substituted with a halogen, nitro, trifluoromethyl, trifluoromethoxy or phenyl or tetrazole-substituted phenyl, and an alkyl that is optionally substituted with a group according to the formula  $BOR_{VI-22}$ , wherein

- 20  $R_{VI-22}$  denotes a straight-chain or branched acyl containing up to 4 carbon atoms or benzyl, or

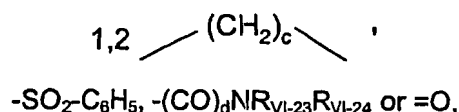
- 25  $R_{VI-19}$  denotes a straight-chain or branched acyl containing up to 20 carbon atoms or benzoyl, which is optionally substituted with a halogen, trifluoromethyl, nitro or trifluoromethoxy, or a straight-chain or branched fluoroacyl containing up to 8 carbon atoms,

$R_{VI-20}$  and  $R_{VI-21}$  are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms, or

- 30  $R_{VI-20}$  and  $R_{VI-21}$  together form a 3- to 6-membered carbocyclic ring, and the carbocyclic rings formed are optionally substituted, optionally also geminally, with up to six identical or different substituents in the form of trifluoromethyl, hydroxyl, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy containing 3 to 7 carbon atoms each, a straight-chain or branched alkoxy carbonyl, alkoxy or alkylthio

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containing up to 6 carbon atoms each, or a straight-chain or branched alkyl containing up to 6 carbon atoms, which is in turn substituted with up to two identical or different substituents in the form of a hydroxyl, benzyloxy, trifluoromethyl, benzoyl, a straight-chain or branched alkoxy, oxyacyl or carboxyl containing up to 4 carbon atoms each and/or a phenyl, which may in turn be substituted with a halogen, trifluoromethyl or trifluoromethoxy, and/or the carbocyclic rings formed are optionally substituted, also geminally, with up to five identical or different substituents in the form of a phenyl, benzoyl, thiophenyl or sulfonylbenzyl, which in turn are optionally substituted with a halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or optionally in the form of a radical according to the formula

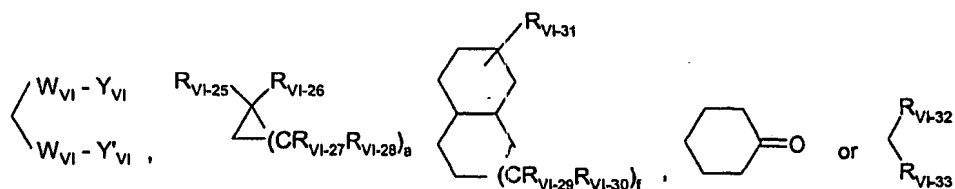


wherein

c is a number equaling 1, 2, 3 or 4,

15 d is a number equaling 0 or 1,

$\text{R}_{\text{VI-23}}$  and  $\text{R}_{\text{VI-24}}$  are identical or different and denote a hydrogen, cycloalkyl containing 3 to 6 carbon atoms, a straight-chain or branched alkyl containing up to 6 carbon atoms, benzyl or phenyl, which is optionally substituted with up to two identical or different substituents in the form of halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the carbocyclic rings formed are optionally substituted with a spiro-linked radical according to the formula



wherein

$\text{W}_{\text{VI}}$  denotes either an oxygen atom or a sulfur atom,

25  $\text{Y}_{\text{VI}}$  and  $\text{Y}'_{\text{VI}}$  together form a 2- to 6-membered straight-chain or branched alkylene chain,

e is a number equaling 1, 2, 3, 4, 5, 6 or 7,

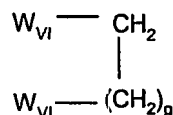
f is a number equaling 1 or 2,

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$R_{VI-25}$ ,  $R_{VI-26}$ ,  $R_{VI-27}$ ,  $R_{VI-28}$ ,  $R_{VI-29}$ ,  $R_{VI-30}$  and  $R_{VI-31}$  are identical or different and denote a hydrogen, trifluoromethyl, phenyl, halogen or a straight-chain or branched alkyl or alkoxy containing up to 6 carbon atoms each, or

5  $R_{VI-25}$  and  $R_{VI-26}$  or  $R_{VI-27}$  and  $R_{VI-28}$  each together denote a straight-chain or branched alkyl chain containing up to 6 carbon atoms or

$R_{VI-25}$  and  $R_{VI-26}$  or  $R_{VI-27}$  and  $R_{VI-28}$  each together form a radical according to the formula



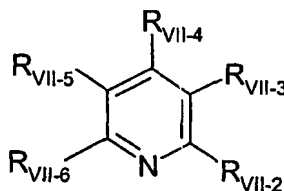
wherein

10  $W_{VI}$  has the meaning given above,

$g$  is a number equaling 1, 2, 3, 4, 5, 6 or 7,

$R_{VI-32}$  and  $R_{VI-33}$  together form a 3- to 7-membered heterocycle, which contains an oxygen or sulfur atom or a group according to the formula  $SO$ ,  $SO_2$  or  $BNR_{VI-34}$ , wherein

15  $R_{VI-34}$  denotes a hydrogen atom, a phenyl, benzyl, or a straight-chain or branched alkyl containing up to 4 carbon atoms, and salts and N oxides thereof, with the exception of 5(6H)-quinolones, 3-benzoyl-7,8-dihydro-2,7,7-trimethyl-4-phenyl;  
(7) a substituted-pyridine having the Formula VII



20

Formula VII

or a pharmaceutically acceptable salt or tautomer thereof,  
wherein

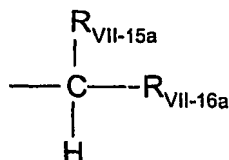
25  $R_{VII-2}$  and  $R_{VII-6}$  are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of  $R_{VII-2}$  and  $R_{VII-6}$  is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R<sub>VII-3</sub> is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl

**-CHO,**

-CO<sub>2</sub>R<sub>VII-7</sub>, wherein R<sub>VII-7</sub> is selected from the group consisting of hydrogen, alkyl and

5 cyanoalkyl; and



wherein R<sub>VII-15a</sub> is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy, and

10  $R_{VII-16a}$  is selected from the group consisting of alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heteroaryl, and heterocyclyl, arylalkoxy, trialkylsilyloxy;

R<sub>VII-4</sub> is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl,

heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy, heteroaroyloxy, heterocyclyloyloxy, alkoxycarbonyl, alkenoxycarbonyl, 20 alkinoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, 25 heterocyclythioalkenyl, alkylamino, alkenylamino, alkynylamino, arylamino, heteroarylamino, heterocyclylamino, arylidialkylamino, diarylamino, diheteroarylamino, alkylarylamino, alkylheteroarylamino, arylheteroarylamino, trialkylsilyl, trialkenylsilyl, triarylsilyl,

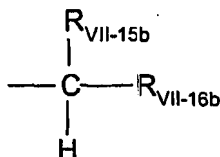
30 -CO(O)N(R<sub>VII-8a</sub>R<sub>VII-8b</sub>), wherein R<sub>VII-8a</sub> and R<sub>VII-8b</sub> are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl.

-SO<sub>2</sub>R<sub>VII-9</sub>, wherein R<sub>VII-9</sub> is selected from the group consisting of hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, -OP(O)(OR<sub>VII-10a</sub>)(OR<sub>VII-10b</sub>),

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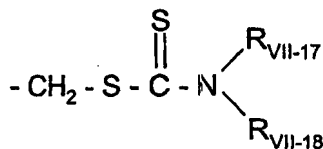
wherein  $R_{VII-10a}$  and  $R_{VII-10b}$  are independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and -OP(S) ( $OR_{VII-11a}$ ) ( $OR_{VII-11b}$ ), wherein  $R_{VII-11a}$  and  $R_{VII-11b}$  are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

- 5  $R_{VII-5}$  is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclioxy, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocyclioxyalkyl, alkoxyalkenyl, alkenoxyalkenyl, alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl, heterocyclioxyalkenyl, cyano, hydroxymethyl,  $-CO_2R_{VII-14}$ , wherein  $R_{VII-14}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;
- 20



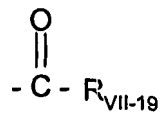
- wherein  $R_{VII-15b}$  is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclioxy, aryloxy, and alkylsulfonyloxy, and
- 25

$R_{VII-16b}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;



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wherein  $R_{VII-17}$  and  $R_{VII-18}$  are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



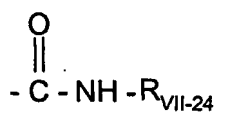
5 wherein  $R_{VII-19}$  is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl,  $-\text{SR}_{VII-20}$ ,  $-\text{OR}_{VII-21}$ , and  $\text{BR}_{VII-22}\text{CO}_2\text{R}_{VII-23}$ , wherein

$R_{VII-20}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroaryl amino, arylheteroaryl amino,

10  $R_{VII-21}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl,

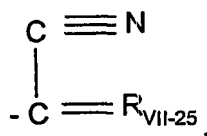
$R_{VII-22}$  is selected from the group consisting of alkylene or arylene, and

$R_{VII-23}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



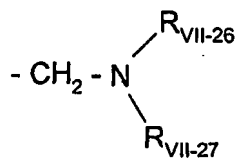
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wherein  $R_{VII-24}$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, aralkenyl, and aralkynyl;



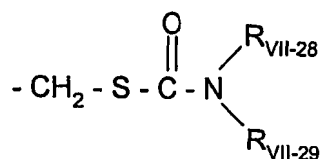
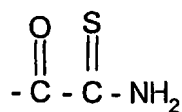
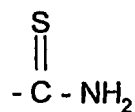
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wherein  $R_{VII-25}$  is heterocyclidenyl;

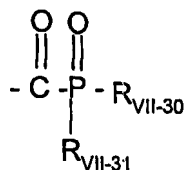


wherein  $R_{VII-26}$  and  $R_{VII-27}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

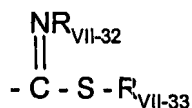
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- wherein  $\text{R}_{\text{VII-28}}$  and  $\text{R}_{\text{VII-29}}$  are independently selected from the group  
 5 consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

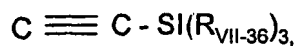
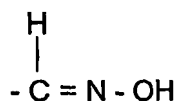


wherein  $\text{R}_{\text{VII-30}}$  and  $\text{R}_{\text{VII-31}}$  are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclyloxy; and



10

wherein  $\text{R}_{\text{VII-32}}$  and  $\text{R}_{\text{VII-33}}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

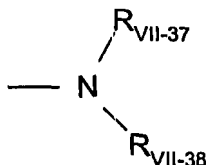


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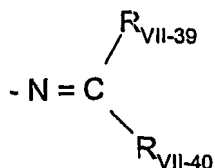
wherein  $\text{R}_{\text{VII-36}}$  is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and heterocyclyl;



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wherein  $\text{R}_{\text{VII-37}}$  and  $\text{R}_{\text{VII-38}}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



5

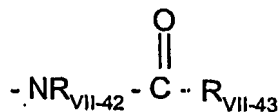
wherein  $\text{R}_{\text{VII-39}}$  is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocycloxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclithio, and

$\text{R}_{\text{VII-40}}$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxy, heterocyclylalkenoxy, heterocyclylalkynoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclithio;

10



wherein  $\text{R}_{\text{VII-41}}$  is heterocyclidenyl;

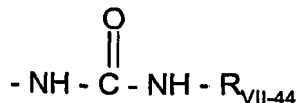


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wherein  $\text{R}_{\text{VII-42}}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, and

$\text{R}_{\text{VII-43}}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, and haloheterocyclyl;

20



wherein  $\text{R}_{\text{VII-44}}$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



25

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- N = C = O;

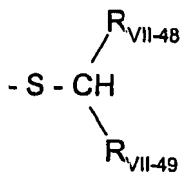
- N<sub>3</sub>;- SR<sub>VII-45</sub>

- wherein R<sub>VII-45</sub> is selected from the group consisting of hydrogen, alkyl,  
 5 alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl,  
 haloaryl, haloheteroaryl, haloheterocyclyl, heterocyclyl, cycloalkylalkyl,  
 cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclalkyl, cycloalkylalkenyl,  
 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclalkenyl, alkylthioalkyl,  
 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl,  
 10 heterocyclthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,  
 arylthioalkenyl, heteroarylthioalkenyl, heterocyclthioalkenyl, aminocarbonylalkyl,  
 aminocarbonylalkenyl, aminocarbonylalkynyl, aminocarbonylaryl,  
 aminocarbonylheteroaryl, and aminocarbonylheterocyclyl,

-SR<sub>VII-46</sub>, and -CH<sub>2</sub>R<sub>VII-47</sub>,

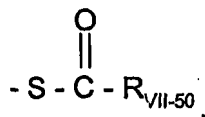
- 15 wherein R<sub>VII-46</sub> is selected from the group consisting of alkyl, alkenyl, alkynyl,  
 aryl, heteroaryl and heterocyclyl, and

R<sub>VII-47</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl,  
 alkynyl, aryl, heteroaryl and heterocyclyl; and



- 20 wherein R<sub>VII-48</sub> is selected from the group consisting of hydrogen, alkyl,  
 cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

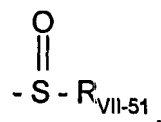
R<sub>VII-49</sub> is selected from the group consisting of alkoxy, alkenoxy, alkynoxy,  
 aryloxy, heteroaryloxy, heterocycloxy, haloalkyl, haloalkenyl, haloalkynyl, haloaryl,  
 haloheteroaryl and haloheterocyclyl;



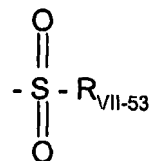
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wherein R<sub>VII-50</sub> is selected from the group consisting of hydrogen, alkyl,  
 cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy,  
 aryloxy, heteroaryloxy and heterocycloxy;

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wherein  $\text{R}_{\text{VII-51}}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and



5

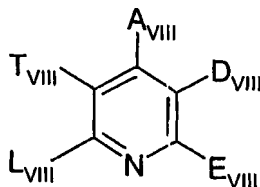
wherein  $\text{R}_{\text{VII-53}}$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

provided that when  $\text{R}_{\text{VII-5}}$  is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the

10 corresponding heterocyclylalkyl or heterocyclylalkenyl is other than  $\delta$ -lactone; and

provided that when  $\text{R}_{\text{VII-4}}$  is aryl, heteroaryl or heterocyclyl, and one of  $\text{R}_{\text{VII-2}}$  and  $\text{R}_{\text{VII-6}}$  is trifluoromethyl, then the other of  $\text{R}_{\text{VII-2}}$  and  $\text{R}_{\text{VII-6}}$  is difluoromethyl;

(8) a substituted pyridine having the Formula VIII



Formula VIII

15 or a pharmaceutically acceptable salt, enantiomer, or stereoisomer thereof, in which

$\text{A}_{\text{VIII}}$  stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or

20 alkoxy with up to 7 carbon atoms each, or by a group of the formula

$-\text{NR}_{\text{VIII-1}}\text{R}_{\text{VIII-2}}$ , wherein

$\text{R}_{\text{VIII-1}}$  and  $\text{R}_{\text{VIII-2}}$  are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 6 carbon atoms,

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D<sub>VIII</sub> stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,

E<sub>VIII</sub> and L<sub>VIII</sub> are either identical or different and stand for straight-chain or branched alkyl with up to 8 carbon atoms, which is optionally substituted by  
 5 cycloalkyl with 3 to 8 carbon atoms, or stands for cycloalkyl with 3 to 8 carbon atoms, or

E<sub>VIII</sub> has the above-mentioned meaning and

L<sub>VIII</sub> in this case stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or  
 10 alkoxy with up to 7 carbon atoms each, or by a group of the formula



R<sub>VIII-3</sub> and R<sub>VIII-4</sub> are identical or different and have the meaning given above for R<sub>VIII-1</sub> and R<sub>VIII-2</sub>, or

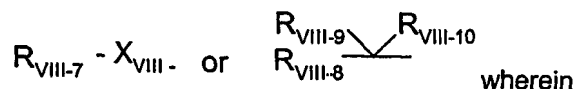
15 E<sub>VIII</sub> stands for straight-chain or branched alkyl with up to 8 carbon atoms, or stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula



R<sub>VIII-5</sub> and R<sub>VIII-6</sub> are identical or different and have the meaning given above for R<sub>VIII-1</sub> and R<sub>VIII-2</sub>, and

L<sub>VIII</sub> in this case stands for straight-chain or branched alkoxy with up to 8 carbon atoms or for cycloalkyloxy with 3 to 8 carbon atoms,

25 T<sub>VIII</sub> stands for a radical of the formula



R<sub>VIII-7</sub> and R<sub>VIII-8</sub> are identical or different and denote cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms, or denote a 5- to 7-member aromatic, optionally benzo-condensed, heterocyclic compound with up to 3  
 30 heteroatoms from the series S, N and/or O, which are optionally substituted up to 3 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, by straight-chain or branched alkyl, acyl, alkoxy, or alkoxycarbonyl with up to 6 carbon atoms each, or by phenyl, phenoxy, or

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thiophenyl, which can in turn be substituted by halogen, trifluoromethyl, or trifluoromethoxy, and/or the rings are substituted by a group of the formula

$-NR_{VIII-11}R_{VIII-12}$ , wherein

$R_{VIII-11}$  and  $R_{VIII-12}$  are identical or different and have the meaning given above  
5 for  $R_{VIII-1}$  and  $R_{VIII-2}$ ,

$X_{VIII}$  denotes a straight or branched alkyl chain or alkenyl chain with 2 to 10 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

$R_{VIII-9}$  denotes hydrogen, and

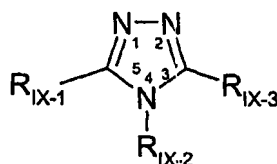
$R_{VIII-10}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, mercapto,  
10 trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula

$-NR_{VIII-13}R_{VIII-14}$ , wherein

$R_{VIII-13}$  and  $R_{VIII-14}$  are identical or different and have the meaning given above  
for  $R_{VIII-1}$  and  $R_{VIII-2}$ , or

15  $R_{VIII-9}$  and  $R_{VIII-10}$  form a carbonyl group together with the carbon atom;

(9) a substituted 1,2,4-triazole having the Formula IX



Formula IX

or a pharmaceutically acceptable salt or tautomer thereof;

wherein  $R_{IX-1}$  is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl,  
20 aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein  $R_{IX-2}$  is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl,  
wherein

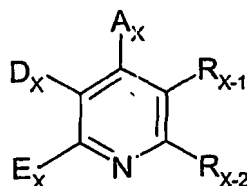
$R_{IX-2}$  is optionally substituted at a substitutable position with one or more radicals  
independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl,  
25 alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino  
and dialkylamino; and

wherein  $R_{IX-3}$  is selected from hydrido, -SH and halo;

provided  $R_{IX-2}$  cannot be phenyl or 4-methylphenyl when  $R_{IX-1}$  is higher alkyl and  
when  $R_{IX-3}$  is BSH;

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(10) a hetero-tetrahydroquinoline having the Formula X



Formula X

or a pharmaceutically acceptable salt, enantiomer, or stereoisomer or N-oxide of said compound;

5 in which

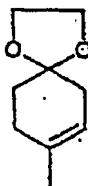
$A_X$  represents cycloalkyl with 3 to 8 carbon atoms or a 5 to 7-membered, saturated, partially saturated or unsaturated, optionally benzo-condensed heterocyclic ring containing up to 3 heteroatoms from the series comprising S, N and/or O, that in case of a saturated heterocyclic ring is bonded to a nitrogen

10 function, optionally bridged over it, and in which the aromatic systems mentioned above are optionally substituted up to 5-times in an identical or different substituents in the form of halogen, nitro, hydroxy, trifluoromethyl, trifluoromethoxy or by a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy each having up to 7 carbon atoms or by a group of the formula  $BNR_{X-3}R_{X-4}$ ,

15 in which

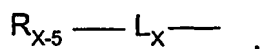
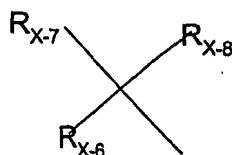
$R_{X-3}$  and  $R_{X-4}$  are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,  
or

$A_X$  represents a radical of the formula

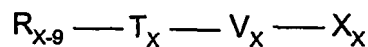


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$D_x$  represents an aryl having 6 to 10 carbon atoms, that is optionally substituted by phenyl, nitro, halogen, trifluormethyl or trifluoromethoxy, or it represents a radical of the formula



or



5 in which

$R_{X-5}$ ,  $R_{X-6}$  and  $R_{X-9}$  independently of one another denote cycloalkyl having 3 to 6 carbon atoms, or an aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-condensed saturated or unsaturated, mono-, bi-, or tricyclic heterocyclic ring from the series consisting of S, N and/or O, in which the rings are substituted, optionally, in case of the nitrogen containing aromatic rings via the N function, with up to 5 identical or different substituents in the form of halogen, trifluoromethyl, nitro, hydroxy, cyano, carbonyl, trifluoromethoxy, straight chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy, or alkoxy carbonyl each having up to 6 carbon atoms, by aryl or trifluoromethyl-substituted aryl each having 6 to 10 carbon atoms or by an, optionally benzo-condensed, aromatic 5- to 7-membered heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N, and/or O, and/or substituted by a group of the formula  $BOR_{X-10}$ ,  $-SR_{X-11}$ ,  $SO_2R_{X-12}$  or  $BNR_{X-13}R_{X-14}$ ,

in which

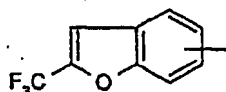
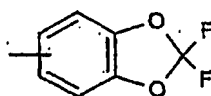
20  $R_{X-10}$ ,  $R_{X-11}$  and  $R_{X-12}$  independently from each other denote aryl having 6 to 10 carbon atoms, which is in turn substituted with up to 2 identical or different substituents in the form of phenyl, halogen or a straight-chain or branched alkyl having up to 6 carbon atoms,

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$R_{X-13}$  and  $R_{X-14}$  are identical or different and have the meaning of  $R_{X-3}$  and  $R_{X-4}$  indicated above,

or

$R_{X-5}$  and/or  $R_{X-6}$  denote a radical of the formula



5

or

$R_{X-7}$  denotes hydrogen or halogen, and

$R_{X-8}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl having up to 6 carbon atoms or a radical of the formula

10

$BNR_{X-15}R_{X-16}$ ,

in which

$R_{X-15}$  and  $R_{X-16}$  are identical or different and have the meaning of  $R_{X-3}$  and  $R_{X-4}$  indicated above,

15

or

$R_{X-7}$  and  $R_{X-8}$  together form a radical of the formula  $=O$  or  $=NR_{X-17}$ ,

in which

$R_{X-17}$  denotes hydrogen or straight chain or branched alkyl, alkoxy or acyl having up to 6 carbon atoms,

20

$L_X$  denotes a straight chain or branched alkylene or alkenylene chain having up to 8 carbon atoms, that are optionally substituted with up to 2 hydroxy groups,

$T_X$  and  $X_X$  are identical or different and denote a straight chain or branched alkylene chain with up to 8 carbon atoms

or

25

$T_X$  or  $X_X$  denotes a bond,

$V_X$  represents an oxygen or sulfur atom or an  $BNR_{X-18}$ -group, in which

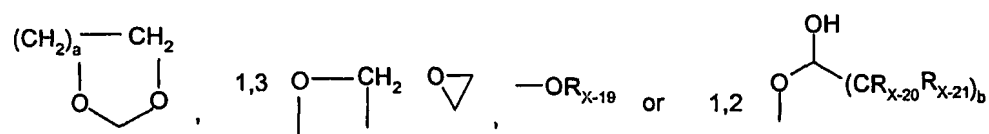


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$R_{X-18}$  denotes hydrogen or straight chain or branched alkyl with up to 6 carbon atoms or phenyl,

$E_X$  represents cycloalkyl with 3 to 8 carbon atoms, or straight chain or branched alkyl with up to 8 carbon atoms, that is optionally substituted by cycloalkyl with 3 to 8 carbon atoms or hydroxy, or represents a phenyl, that is optionally substituted by halogen or trifluoromethyl,

$R_{X-1}$  and  $R_{X-2}$  together form a straight-chain or branched alkylene chain with up to 7 carbon atoms, that must be substituted by carbonyl group and/or by a radical with the formula



in which a and b are identical or different and denote a number equaling 1,2, or 3,

$R_{X-19}$  denotes hydrogen, cycloalkyl with 3 up to 7 carbon atoms, straight chain or branched silylalkyl with up to 8 carbon atoms or straight chain or branched alkyl with up to 8 carbon atoms, that are optionally substituted by hydroxyl, straight chain or branched alkoxy with up to 6 carbon atoms or by phenyl, which in turn might be substituted by halogen, nitro, trifluoromethyl, trifluoromethoxy or by phenyl or by tetrazole-substituted phenyl, and alkyl, optionally be substituted by a group with the formula  $BOR_{X-22}$ , in which

$R_{X-22}$  denotes a straight chain or branched acyl with up to 4 carbon atoms or benzyl, or

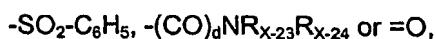
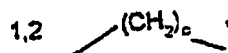
$R_{X-19}$  denotes straight chain or branched acyl with up to 20 carbon atoms or benzoyl, that is optionally substituted by halogen, trifluoromethyl, nitro or trifluoromethoxy, or it denotes straight chain or branched fluoroacyl with up to 8 carbon atoms and 9 fluorine atoms,

$R_{X-20}$  and  $R_{X-21}$  are identical or different and denote hydrogen, phenyl or straight chain or branched alkyl with up to 6 carbon atoms, or

$R_{X-20}$  and  $R_{X-21}$  together form a 3- to 6- membered carbocyclic ring, and the carbocyclic rings formed are optionally substituted, optionally also geminally, with up to six identical or different substituents in the form of trifluoromethyl, hydroxy, nitrile,

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halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy with 3 to 7 carbon atoms each, by straight chain or branched alkoxy carbonyl, alkoxy or alkylthio with up to 6 carbon atoms each or by straight chain or branched alkyl with up to 6 carbon atoms, which in turn is substituted with up to 2 identically or differently by hydroxyl, benzyloxy, trifluoromethyl, benzoyl, straight chain or branched alkoxy, oxyacyl or carbonyl with up to 4 carbon atoms each and/or phenyl, which may in turn be substituted with a halogen, trifluoromethyl or trifluoromethoxy, and/or the formed carbocyclic rings are optionally substituted, also geminally, with up to 5 identical or different substituents in the form of phenyl, benzoyl, thiophenyl or sulfonylbenzyl, which in turn are optionally substituted by halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or optionally are substituted by a radical with the formula

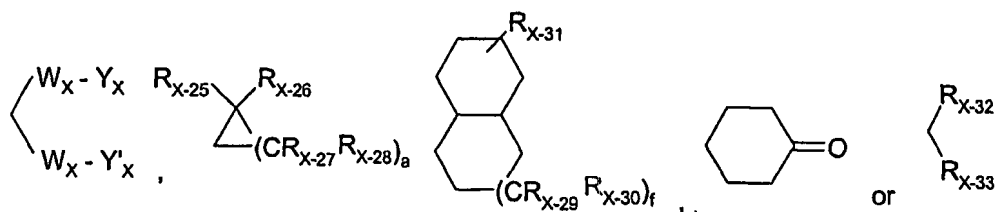


in which

$c$  denotes a number equaling 1, 2, 3, or 4,

$d$  denotes a number equaling 0 or 1,

$\text{R}_{X-23}$  and  $\text{R}_{X-24}$  are identical or different and denote hydrogen, cycloalkyl with 3 to 6 carbon atoms, straight chain or branched alkyl with up to 6 carbon atoms, benzyl or phenyl, that is optionally substituted with up to 2 identically or differently by halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the formed carbocyclic rings are substituted optionally by a spiro-linked radical with the formula



in which

$\text{W}_X$  denotes either an oxygen or a sulfur atom

$\text{Y}_X$  and  $\text{Y}'_X$  together form a 2 to 6 membered straight chain or branched alkylene chain,

$e$  denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

$f$  denotes a number equaling 1 or 2,

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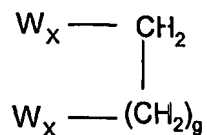
$R_{X-25}$ ,  $R_{X-26}$ ,  $R_{X-27}$ ,  $R_{X-28}$ ,  $R_{X-29}$ ,  $R_{X-30}$  and  $R_{X-31}$  are identical or different and denote hydrogen, trifluoromethyl, phenyl, halogen or straight chain or branched alkyl or alkoxy with up to 6 carbon atoms each,

or

$R_{X-25}$  and  $R_{X-26}$  or  $R_{X-27}$  and  $R_{X-28}$  respectively form together a straight chain or branched alkyl chain with up to 6 carbon atoms,

or

$R_{X-25}$  and  $R_{X-26}$  or  $R_{X-27}$  and  $R_{X-28}$  each together form a radical with the formula



in which

$W_X$  has the meaning given above,

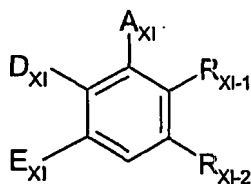
$g$  denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

$R_{X-32}$  and  $R_{X-33}$  form together a 3- to 7- membered heterocycle, which contains an oxygen or sulfur atom or a group with the formula  $\text{SO}$ ,  $\text{SO}_2$  or-  $\text{NR}_{X-34}$ ,

in which

$R_{X-34}$  denotes hydrogen, phenyl, benzyl or straight or branched alkyl with up to 4 carbon atoms;

(11) a substituted tetrahydro naphthaline or an analogous compound having the Formula XI



Formula XI

or a stereoisomer, stereoisomeric mixture, or salt thereof, in which

$A_{XI}$  stands for cycloalkyl with 3 to 8 carbon atoms, or stands for aryl with 6 to 10 carbon atoms, or stands for a 5- to 7-membered, saturated, partially unsaturated or unsaturated, possibly benzocondensated, heterocycle with up to 4 heteroatoms from the series S, N and/or O, where aryl and the heterocyclic ring systems mentioned above are

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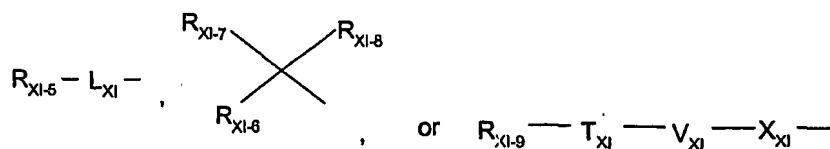
substituted up to 5-fold, identical or different, by cyano, halogen, nitro, carboxyl, hydroxy, trifluoromethyl, trifluoro-methoxy, or by straight-chain or branched alkyl, acyl, hydroxyalkyl, alkylthio, alkoxycarbonyl, oxyalkoxycarbonyl or alkoxy each with up to 7 carbon atoms, or by a group of the formula



in which

$\text{R}_{\text{XI}-3}$  and  $\text{R}_{\text{XI}-4}$  are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 6 carbon atoms

$\text{D}_{\text{XI}}$  stands for a radical of the formula



in which

$\text{R}_{\text{XI}-5}$ ,  $\text{R}_{\text{XI}-6}$  and  $\text{R}_{\text{XI}-9}$ , independent of each other, denote cycloalkyl with 3 to 6 carbon atoms, or denote aryl with 6 to 10 carbon atoms, or denote a 5- to 7-membered, possibly benzocondensated, saturated or unsaturated, mono-, bi- or tricyclic heterocycle with up to 4 heteroatoms of the series S, N and/or O, where the cycles are possibly substituted. In the case of the nitrogen-containing rings also via the N-function. Up to 5-fold, identical or different, by halogen, trifluoromethyl, nitro, hydroxy, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl with up to 6 carbon atoms each. by aryl or trifluoromethyl substituted aryl with 6 to 10 carbon atoms each, or by a possibly benzocondensated aromatic 5- to 7-membered heterocycle with up to 3 heteroatoms of the series S, N and/or O, and/or are substituted by a group of the formula



in which

$\text{R}_{\text{XI}-10}$ ,  $\text{R}_{\text{XI}-11}$  and  $\text{R}_{\text{XI}-12}$ , independent of each other, denote aryl with 6 to 10 carbon atoms, which itself is substituted up to 2-fold, identical or different, by phenyl, halogen, or by straight-chain or branched alkyl with up to 6 carbon atoms,

$\text{R}_{\text{XI}-13}$  and  $\text{R}_{\text{XI}-14}$  are identical or different and have the meaning given above for  $\text{R}_{\text{XI}-3}$  and  $\text{R}_{\text{XI}-4}$ ,

or

$\text{R}_{\text{XI}-5}$  and/or  $\text{R}_{\text{XI}-6}$  denote a radical of the formula

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$R_{Xl-7}$  denotes hydrogen, halogen or methyl,

and

$R_{Xl-8}$  denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl with up to 6 carbon atoms each, or a radical of the formula  $-NR_{Xl-15}R_{Xl-16}$ ,

in which

$R_{Xl-15}$  and  $R_{Xl-16}$  are identical or different and have the meaning given above for  $R_{Xl-3}$  and  $R_{Xl-4}$ ,

or

$R_{Xl-7}$  and  $R_{Xl-8}$  together form a radical of the formula  $=O$  or  $=NR_{Xl-17}$ , in which

$R_{Xl-17}$  denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl with up to 6 carbon atoms each,

$L_{Xl}$  denotes a straight-chain or branched alkylene- or alkenylene chain with up to 8 carbon atoms each, which is possibly substituted up to 2-fold by hydroxy,

$T_{Xl}$  and  $X_{Xl}$  are identical or different and denote a straight-chain or branched alkylene chain with up to 8 carbon atoms,

or

$T_{Xl}$  and  $X_{Xl}$  denotes a bond,

$V_{Xl}$  stands for an oxygen- or sulfur atom or for an  $-NR_{Xl-18}$  group,

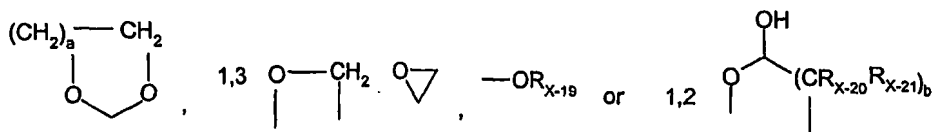
in which

$R_{Xl-18}$  denotes hydrogen or straight-chain or branched alkyl with up to 6 carbon atoms, or phenyl,

$E_{Xl}$  stands for cycloalkyl with 3 to 8 carbon atoms, or stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or hydroxy, or stands for phenyl, which is possibly substituted by halogen or trifluoromethyl,

$R_{Xl-1}$  and  $R_{Xl-2}$  together form a straight-chain or branched alkylene chain with up to 7 carbon atoms, which must be substituted by a carbonyl group and/or by a radical of the formula

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in which

a and b are identical or different and denote a number 1, 2 or 3

$R_{X1-19}$  denotes hydrogen, cycloalkyl with 3 to 7 carbon atoms, straight-chain or branched silylalkyl with up to 8 carbon atoms, or straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by hydroxy, straight-chain or branched alkoxy with up to 6 carbon atoms, or by phenyl, which itself can be substituted by halogen, nitro, trifluoromethyl, trifluoromethoxy or by phenyl substituted by phenyl or tetrazol, and alkyl is possibly substituted by a group of the formula  $-OR_{X1-22}$ ,

in which

$R_{X1-22}$  denotes straight-chain or branched acyl with up to 4 carbon atoms, or benzyl,

or

$R_{X1-19}$  denotes straight-chain or branched acyl with up to 20 carbon atoms or benzoyl, which is possibly substituted by halogen, trifluoromethyl, nitro or trifluoromethoxy, or denotes straight-chain or branched fluoroacyl with up to 8 carbon atoms and 9 fluorine atoms,

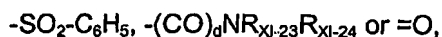
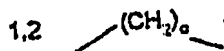
$R_{X1-20}$  and  $R_{X1-21}$  are identical or different, denoting hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

or

$R_{X1-20}$  and  $R_{X1-21}$  together form a 3- to 6-membered carbocycle, and, possibly also geminally, the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$ , is possibly substituted up to 6-fold, identical or different, by trifluoromethyl, hydroxy, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy with 3 to 7 carbon atoms each, by straight-chain or branched alkoxy, carbonyl, alkoxy or alkoxythio with up to 6 carbon atoms each, or by straight-chain or branched alkyl with up to 6 carbon atoms, which itself is substituted up to 2-fold, identical or different, by hydroxyl, benzyloxy, trifluoromethyl, benzoyl, straight-chain or branched alkoxy, oxyacyl or carboxyl with up to 4 carbon atoms each, and/or phenyl- which itself can be substituted by halogen, trifluoromethyl or trifluoromethoxy, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is substituted, also geminally, possibly up to 5-fold, identical or different, by phenyl, benzoyl, thiophenyl or

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sulfobenzyl -which themselves are possibly substituted by halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is possibly substituted by a radical of the formula

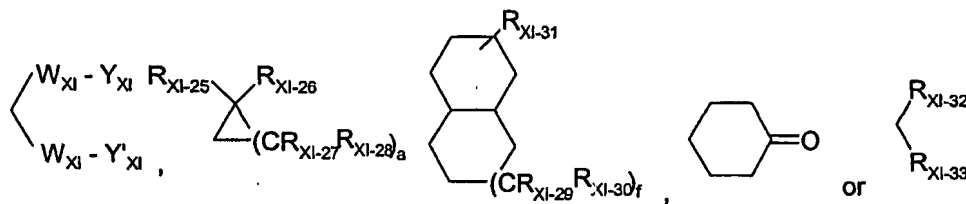


in which

$c$  denotes a number 1, 2, 3 or 4,

$d$  denotes a number 0 or 1,

$R_{X1-23}$  and  $R_{X1-24}$  are identical or different and denote hydrogen, cycloalkyl with 3 to 6 carbon atoms, straight-chain or branched alkyl with up to 6 carbon atoms, benzyl or phenyl, which is possibly substituted up to 2-fold, identical or different, by halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the alkylene chain formed by  $R_{X1-1}$  and  $R_{X1-2}$  is possibly substituted by a spiro-jointed radical of the formula



in which

$W_{X1}$  denotes either an oxygen or a sulfur atom,

$Y_{X1}$  and  $Y'_{X1}$  together form a 2- to 6-membered straight-chain or branched alkylene chain,

$e$  is a number 1, 2, 3, 4, 5, 6 or 7,

$f$  denotes a number 1 or 2,

$R_{X1-25}$ ,  $R_{X1-26}$ ,  $R_{X1-27}$ ,  $R_{X1-28}$ ,  $R_{X1-29}$ ,  $R_{X1-30}$  and  $R_{X1-31}$  are identical or different and denote hydrogen, trifluoromethyl, phenyl, halogen, or straight-chain or branched alkyl or alkoxy with up to 6 carbon atoms each,

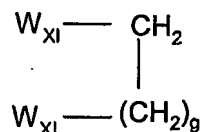
or

$R_{X1-25}$  and  $R_{X1-26}$  or  $R_{X1-27}$  and  $R_{X1-28}$  together form a straight-chain or branched alkyl chain with up to 6 carbon atoms,

or

$R_{X1-25}$  and  $R_{X1-26}$  or  $R_{X1-27}$  and  $R_{X1-28}$  together form a radical of the formula

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in which

$W_{XI}$  has the meaning given above,

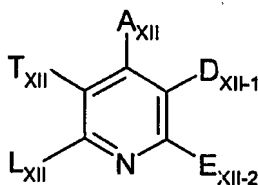
$g$  is a number 1, 2, 3, 4, 5, 6 or 7,

$R_{XI-32}$  and  $R_{XI-33}$  together form a 3- to 7-membered heterocycle that contains an oxygen- or sulfur atom or a group of the formula  $SO$ ,  $SO_2$  or  $-NR_{XI-34}$ ,

in which

$R_{XI-34}$  denotes hydrogen, phenyl, benzyl, or straight-chain or branched alkyl with up to 4 carbon atoms;

(12) a 2-aryl-substituted pyridine having the Formula (XII)



Formula XII

or pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds,

in which

$A_{XII}$  and  $E_{XII}$  are identical or different and stand for aryl with 6 to 10 carbon atoms which is possibly substituted, up to 5-fold identical or different, by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, nitro or by straight-chain or branched alkyl, acyl, hydroxy alkyl or alkoxy with up to 7 carbon atoms each, or by a group of the formula - $NR_{XII-1}R_{XII-2}$ ,

where

$R_{XII-1}$  and  $R_{XII-2}$  are identical or different and are meant to be hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

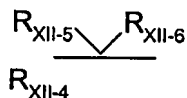
$D_{XII}$  stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,



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$L_{XII}$  stands for cycloalkyl with 3 to 8 carbon atoms or for straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms, or by hydroxy,

$T_{XII}$  stands for a radical of the formula  $R_{XII-3}-X_{XII}-$  or



where

$R_{XII-3}$  and  $R_{XII-4}$  are identical or different and are meant to be cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms, or a 5- to 7-membered aromatic, possibly benzocondensated heterocycle with up to 3 heteroatoms from the series S, N and/or O, which are possibly substituted. up to 3-fold identical or different, by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, nitro, by straight-chain or branched alkyl, acyl, alkoxy or alkoxycarbonyl with up to 6 carbon atoms each. or by phenyl, phenoxy or phenylthio which in turn can be substituted by halogen. trifluoromethyl or trifluoromethoxy, and/or where the cycles are possibly substituted by a group of the formula  $-NR_{XII-7}R_{XII-8}$ ,

where

$R_{XII-7}$  and  $R_{XII-8}$  are identical or different and have the meaning of  $R_{XII-1}$  and  $R_{XII-2}$  given above,

$X_{XII}$  is a straight-chain or branched alkyl or alkenyl with 2 to 10 carbon atoms each, possibly substituted up to 2-fold by hydroxy or halogen,

$R_{XII-5}$  stands for hydrogen,

and

$R_{XII-6}$  means to be hydrogen, halogen, mercapto, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula  $BNR_{XII-9}R_{XII-10}$ ,

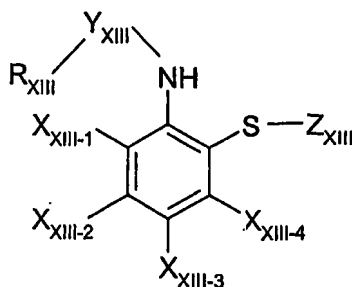
where

$R_{XII-9}$  and  $R_{XII-10}$  are identical or different and have the meaning of  $R_{XII-1}$  and  $R_{XII-2}$  given above,

or

$R_{XII-5}$  and  $R_{XII-6}$ , together with the carbon atom, form a carbonyl group; or  
(13) a compound having the Formula (XIII)

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Formula XIII

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, hydrate, or solvate of said compounds, in which

$R_{XIII}$  is a straight chain or branched  $C_{1-10}$  alkyl; straight chain or branched  $C_{2-10}$  alkenyl; halogenated  $C_{1-4}$  lower alkyl;  $C_{3-10}$  cycloalkyl that may be substituted;  $C_{5-8}$  cycloalkenyl that may be substituted;  $C_{3-10}$  cycloalkyl  $C_{1-10}$  alkyl that may be substituted; aryl that may be substituted; aralkyl that may be substituted; or a 5- or 6-membered heterocyclic group having 1 to 3 nitrogen atoms, oxygen atoms or sulfur atoms that may be substituted,

$X_{XIII-1}$ ,  $X_{XIII-2}$ ,  $X_{XIII-3}$ ,  $X_{XIII-4}$  may be the same or different and are a hydrogen atom; halogen atom;  $C_{1-4}$  lower alkyl; halogenated  $C_{1-4}$  lower alkyl;  $C_{1-4}$  lower alkoxy; cyano group; nitro group; acyl; or aryl, respectively;

$Y_{XIII}$  is  $-CO-$ ; or  $BSO_2-$ ; and

$Z_{XIII}$  is a hydrogen atom; or mercapto protective group.

9. A composition as defined in claim 8, wherein said CETP inhibitor is selected from:

[2R,4S] 4-[(3,5-dichloro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-dinitro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(2,6-dichloro-pyridin-4-ylmethyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

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- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-ethoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoro-ethylester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
- [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyryl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester;
- [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester;
- [2R,4S] (3,5-bis-trifluoromethyl-benzyl)-[1-(2-ethyl-butyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid methyl ester, hydrochloride;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2,6,7-trimethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

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- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-diethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-ethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R, 4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-2,3,4,6,7,8-hexahydro-cyclopenta[g]quinoline-1-carboxylic acid ethyl ester;
- [6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-1H-2-thia-5-aza-cyclopenta[b]naphthalene-5-carboxylic acid ethylester;
- [6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-2H-furo[2,3-g]quinoline-5-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,8-tetrahydro-2H-furo[3,4-g]quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,7,8,9-hexahydro-2H-benzo[g]quinoline-1-carboxylic acid propyl ester;
- [7R,9S] 9-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methyl-1,2,3,7,8,9-hexahydro-6-aza-cyclopenta[a]naphthalene-6-carboxylic acid ethyl ester;
- [6S,8R] 6-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-methyl-1,2,3,6,7,8-hexahydro-9-aza-cyclopenta[a]naphthalene-9-carboxylic acid ethyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-chloro-2-cyclopropyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 2-cyclopropyl-4-[(3,5-dichloro-benzyl)-methoxycarbonyl-amino]-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;

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- [2R,4R] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclobutyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methoxymethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxy-ethyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester.
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2S,4S] 4-[1-(3,5-bis-trifluoromethyl-benzyl)-ureido]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

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- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methoxymethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
- [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.
- 2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-3-(4-trifluoromethylbenzoyl)-4,6,7,8-tetrahydro-1H-quinolin-5-one;
- 2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-3-(4-trifluoromethylbenzoyl)-7,8-dihydro-6H-quinolin-5-one;
- [2-cyclopentyl-4-(4-fluorophenyl)-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanone;
- [5-(t-butyltrimethylsilyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanone;
- [5-(t-butyltrimethylsilyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl]-(4-trifluoromethylphenyl)-methanol;

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5-(t-butyl dimethylsilanyloxy)-2-cyclopentyl-4-(4-fluorophenyl)-3-[fluoro-(4-trifluoromethylphenyl)-methyl]-7,7-dimethyl-5,6,7,8-tetrahydroquinoline;

2-cyclopentyl-4-(4-fluorophenyl)-3-[fluoro-(4-trifluoromethylphenyl)-methyl]-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-5-ol;

dimethyl 5,5=dithiobis[2-difluoromethyl-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate]

2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-fluorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-cyclohexyl-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-pyridyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-ethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2,6-dimethylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-phenoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(1,3-benzodioxol-5-yl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(2-chlorophenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(3-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(3-fluorophenyl)-3H-1,2,4-triazole-3-thione;

4-(3-chloro-4-methylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(4-benzyloxyphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

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- 2,4-dihydro-4-(2-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-5-tridecyl-4-(4-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(1-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(3-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(4-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(3,4-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(2,5-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(2-methoxy-5-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 4-(4-aminosulfonylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-5-dodecyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(3-methoxyphenyl)-5-tetradecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(3-methoxyphenyl)-5-undecyl-3H-1,2,4-triazole-3-thione;
- 2,4-dihydro-4-(4-methoxyphenyl)-5-pentadecyl-3H-1,2,4-triazole-3-thione;
- 2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(4-trifluoromethylbenzoyl)-5,6,7,8-tetrahydroquinoline;
- 2-cyclopentyl-3-[fluoro-(4-trifluoromethylphenyl)methyl]-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-5,6,7,8-tetrahydroquinoline;
- 2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(trifluoromethylbenzyl)-5,6,7,8-tetrahydroquinoline.
- 4,6-bis-(p-fluorophenyl)-2-isopropyl-3-[(p-trifluoromethylphenyl)-(fluoro)-methyl]-5-(1-hydroxyethyl)pyridine;
- 2,4-bis-(4-fluorophenyl)-6-isopropyl-5-[4-(trifluoromethylphenyl)-fluoromethyl]-3-hydroxymethylpyridine;
- 2,4-bis-(4-fluorophenyl)-6-isopropyl-5-[2-(3-trifluoromethylphenyl)vinyl]-3-hydroxymethylpyridine;



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N,N'-(dithiodi-2,1-phenylene)bis[2,2-dimethyl-propanamide];

N,N'-(dithiodi-2,1-phenylene)bis[1-methyl-cyclohexanecarboxamide];

N,N'-(dithiodi-2,1-phenylene)bis[1-(3-methylbutyl)-cyclopentanecarboxamide];

N,N'-(dithiodi-2,1-phenylene)bis[1-(3-methylbutyl)-cyclohexanecarboxamide];

N,N'-(dithiodi-2,1-phenylene)bis[1-(2-ethylbutyl)-cyclohexanecarboxamide];

N,N'-(dithiodi-2,1-phenylene)bis-tricyclo[3.3.1.<sup>3,7</sup>]decane-1-carboxamide;

propanethioic acid, 2-methyl-, S-[2[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester;

propanethioic acid, 2,2-dimethyl-, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester; and

ethanethioic acid, S-[2-[[[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino]phenyl] ester.

10. A composition comprising:

a compound which is [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; or a compound which is [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester; or a compound which is [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;

a cosolvent;

a high HLB surfactant;

a low HLB surfactant; and

optionally, a digestible oil.

11. A composition as claimed in claim 10, wherein

said cosolvent comprises triacetin or ethyl lactate;

said high HLB surfactant comprises polysorbate 80 or a polyethylene hydrogenated castor oil;

said low HLB surfactant comprises a mixture of mono- and diglycerides of capric and caprylic acids;

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said digestible oil comprises a medium chain triglyceride, wherein each of the three hydrocarbon chains therein is C6-C12.

12. A composition as claimed in claim 11, which comprises, by weight:

- 5 -25% of said CETP inhibitor;
- 10-25% of said digestible oil;
- 20-35% of said cosolvent:
- 10-35% of said high HLB surfactant; and
- 10-35% of said low HLB surfactant;

13. A composition as claimed in claim 10, which comprises, by weight:

- 8-12% of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester
- 10-20% of said digestible oil;
- 25-35% of said cosolvent which is triacetin:
- 10-30% of said high HLB surfactant which is polysorbate 80; and
- 15-35% of said low HLB surfactant.

14. A composition as claimed in claim 10, which comprises, by weight:

- 8-25% of [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 10-25% of digestible oil;
- 20-35% of said cosolvent which comprises triacetin;
- 10-30% of said high HLB surfactant which comprises polysorbate 80; and
- 15-35% of said low HLB surfactant which comprises a mixture of medium chain mono- and di-glycerides.

15. A composition as claimed in claim 43, which comprises, by weight:

- 8-12% of [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
- 10-20% of said digestible oil;
- 25-35% of said cosolvent which comprises triacetin;

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10-30% of said high HLB surfactant which comprises a polyethylene (40)  
hydrogenated castor oil;

15-35% of said low HLB surfactant which comprises a mixture of medium chain  
mono- and di-glycerides.